A STUDY OF DRUG UTILIZATION PATTERN AND ADVERSE DRUG REACTION PROFILE OF ANTIHYPERTENSIVE DRUGS PRESCRIBED IN A TERTIARY CARE HOSPITAL

Dissertation

Submitted to

THE TAMILNADU Dr. M.G.R MEDICAL UNIVERSITY

In partial fulfilment of the requirements for the award of the degree of

M.D PHARMACOLOGY

Branch VI

April 2015

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CERTIFICATE

This is to certify that the dissertation entitled "**A Study of Drug Utilization Pattern and Adverse Drug Reaction Profile of Antihypertensive Drugs Prescribed in A Tertiary Care Hospital**" is a bonafide work done by **Dr. A. Navaneeth,** Sree Mookambika Institute Of Medical Sciences, Kulasekharam, in partial fulfilment of the University rules and regulations for award of **M.D Pharmacology [Branch-VI]** under my guidance and supervision during the academic year 2012-2015.

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ABSTRACT

A Study of Drug Utilization Pattern and Adverse Drug Reaction Profile of Antihypertensive Drugs Prescribed in a Tertiary Care Hospital

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Introduction

Hypertension is an established risk factor for cardiovascular diseases with shortened expectancy of life. In this context, the use of established antihypertensive drugs assumes special importance. Various drug utilization pattern studies have been undertaken to provide useful feedback information to prescribers in order to establish the rational use of antihypertensive drugs. Accordingly, the present study in particular envisages the examination of the prescribing pattern, rationality and ADRs of antihypertensive drugs in a tertiary care hospital.

Aims and objectives

To assess the pattern of prescription of antihypertensive drugs as monotherapy and combination therapy, the pattern by brand name and generic names, pharmacoeconomics of antihypertensive drugs prescribed**,** rationality of antihypertensive drugs prescribed and the adverse drug reaction profile of antihypertensive drugs.

Materials and Methods

A cross-sectional study was conducted in Department of Medicine in a tertiary care hospital over a period of six months. The diagnosis and line of treatment to be given was decided by the treating physician. All the information about ADR was recorded in CDSCO Suspected ADR reporting form.

Results

Out of 127 patients, 74.8% were female and 25.2% were male. Maximum patients belonged to age group of 61-70 years (51.18%). Diabetes mellitus (39.28%) was the most common associated disease with hypertension. About three fourth of the patients had received one antihypertensive drug (75.59%), followed by two (17.32%), three (5.51%) and four (1.58%) antihypertensive drugs. All the drugs were prescribed by brand name. Amlodipine was the most commonly prescribed antihypertensive drug. 86 patients developed ADR to antihypertensive drugs. Metoprolol was the most expensive and furosemide was the least expensive drug prescribed as monotherapy. Amlodipine was responsible for most of the ADRs. ADRs associated with CNS (43.02%) were found to be most frequent. Headache was the commonest ADR followed by dizziness and pedal oedema. Majority of the ADRs were mild (87.21%).

Conclusion

Rational utilization pattern of antihypertensive drugs was observed. However diuretics were prescribed less commonly. Most of the ADRs were mild (87.21%).

Key words: Adverse drug reaction, drug utilization pattern, hypertension

1. Introduction:

Hypertension is a major public health problem due to increased morbidity, mortality and cost to the public.[1] It is a major contributor to the global burden of diseases to the extent of 4.5% and it continues its upward growth trends.[2] In 2000 prevalence of hypertension in India was about 60 million males and 58 million females; it is expected to become 107 million males and 106 million females in 2015. The prevalence of hypertension among urban population (4 - 15%) is more than that among rural population (2 - 8%).[3] It is an iceberg condition and the prevalence of hypertension has been considered as an increasing “silent killer” problem.[4]

Reasons for this growing trend is due to the unhealthy lifestyle practices, lack of awareness, distorted public health system, physicians not following the standard guidelines in treating hypertension and non-compliance to hypertension therapy.[3] Keeping the blood pressure at an optimum level helps to prevent cardiovascular complications like stroke, myocardial infarction (MI), renal failure and mortality; this has been confirmed in epidemiological and interventional studies.[5]

In health economics, the major problems are the need of long term medication and the cost of the drug in the midst of high prevalence of hypertension. In developed countries, recently, there has been a sharp increase in the expenditure on antihypertensive therapy as many new and expensive drugs are coming out. Presence of comorbid conditions like diabetes mellitus

(DM) and hyperlipidemia further increases the treatment cost for the patients due to co-prescribing of long term medications for these conditions as well.[5]

Based on clinical evidence and cost effectiveness, the general principles of antihypertensive drug therapy as per the guidelines of Joint National Committee 7 (JNC 7) and World Health Organization (WHO)–International Society of Hypertension (ISH) are as follows: initially monotherapy is started; subsequently, this is followed by combination therapy if required.[6] Prescription pattern depends on age, gender and other comorbidities.[7] It is recommended that diuretics, particularly the thiazides, are the first line treatment for uncomplicated hypertension. In complicated cases, CCBs and ACE inhibitors are indicated.[8] On other hand, the European guidelines suggests if there is no specific indication, any of the five major classes of antihypertensive drugs can be started as first line treatment.[8] For severe and uncontrolled hypertension, combination therapy is recommended as first line treatment. Many drugs in different combinations are used for long term treatment of hypertension.[8]

Changes overtime due to changes in treatment guidelines and availability of different drug formulations modifies the prescription pattern of antihypertensive drugs; thus, drug utilization studies comes to play. Drug utilization studies (DUS) help to analyze and evaluate the social, medical and economic outcomes of drug treatment; thus, they help to observe the prescribing attitude of physicians ultimately aiming at providing drug rationality; as the treatment is lifelong, the prescription needs special emphasis.[8]

Antihypertensive drugs are more prone for development of adverse drug reactions (ADRs); this decreases the available treatment options and also reduces the compliance of the patients; this in turn hinders blood pressure control.[9] Hypertension is a disorder that requires long term therapy; this predisposes to ADRs.[10] As many studies do not include pregnant ladies, the elderly and patients with many diseases, the study population may not be the real world where drug has to be used eventually; hence, safety monitoring has to be done to get information regarding ADRs to have a better treatment module and to prevent morbidity and mortality due to ADRs.[11] Currently, ADR monitoring in India is in its infancy stage.[10]

Many new antihypertensive drugs are now available, which alter quality of life of the patient in a better way. Thus a regular scrutinization is needed by systematic audit that gives feedback to doctors, which will help to prescribe drugs rationally and to avoid ADRs.[2]

2. Justification:

Regular studies on drug utilization pattern are important to promote prescription of drugs rationally, to increase therapeutic efficacy, to decrease the cost, to decrease the ADRs and to give feedback to the prescribing doctors. Thus the main aim of drug utilization studies is to enable the rational use of drugs in the population. They also help to frame hypotheses that set the outline for further studies and thus help to prevent irrational use of drugs. They create a strong socio-medical and economic foundation for taking decisions regarding healthcare.[8]

At present there is an increasing trend for irrational prescribing of antihypertensive drugs. This will increase the cost burden on the health care system; hence, it is very essential to analyse the prescribing patterns and whether the prescribing doctors are following treatment guidelines.[2]

It is very essential to regularly monitor for ADRs in chronic conditions like hypertension. But DUS and ADR studies have not been reported so far in our institution. Hence, this study was undertaken as data from this part of South India are not much available and lacunae can be filled up to some extent with this study.

3. Aims and objectives:

To assess the following in the Department of Medicine, Sree Mookambika Institute of Medical Sciences, Kulasekharam, Tamilnadu during the period from October 2013 to March 2014:

- The pattern of prescription of antihypertensive drugs as monotherapy and combination therapy
- The pattern by brand name and generic names
- The pharmacoeconomics of antihypertensive drugs prescribed
- Rationality of antihypertensive drugs prescribed
- The adverse drug reaction profile of antihypertensive drugs

4.1. Hypertension:

4.1.1. Introduction[12]:

Hypertension is a long lasting condition of concern as it is responsible for causation of atherosclerotic heart disease and cerebrovascular accident (CVA). It is one of the main risk factors leading to cardiovascular complications.

4.1.2. History[13]:

Thomas Young in 1808 was the first person to describe hypertension as a disease. In 1900, Treupel used sodium thiocyanate in the treatment of hypertension. Fritz Bruening performed the first sympathectomy operation for hypertension in 1923**.** Otto Frank in 1925 introduced the concept of essential hypertension. Physicians from the Mayo Clinic in 1928 coined the term malignant hypertension. In 1957 Freis introduced chlorothiazide in the treatment of hypertension; this was the first orally effective diuretic.

4.1.3. Definition[14]:

Hypertension is defined according to JNC 7 and WHO/ISH guidelines as systolic blood pressure of ≥ 140 mm Hg and diastolic blood pressure of ≥ 90 mm Hg, though the risk appears to increase even with blood pressure above 120/80 mm Hg.

4.1.4. Epidemiology[12,15]:

In developed countries, diastolic pressure is more than 90 mm Hg in about 25% adults; this prevalence is almost same in developing countries,

where it is seen in 10% to 20% adults. Hypertension accounts for 20-50% of all deaths.

Hypertension is present in all populations and it steadily increases during the first two decades of life. With advancing age, the prevalence of hypertension also increases. Systolic blood pressure is higher for adult males than females, but in older individuals, the age related rate rise is steeper for females. A middle aged or elderly individual has 90% chance of developing hypertension in his or her lifetime. Both genetic and environmental factors play a major role to produce regional and racial changes in blood pressure and prevalence of hypertension.

In India the prevalence of hypertension was 35 in males and 36 in females per 1000 in rural population and 60 in males and 70 in females per 1000 in the urban population.

4.1.5. Classification[16]:

4.1.5. A. Essential or primary hypertension:

A patient is said to have essential hypertension when no particular cause of hypertension can be found.

4.1.5. B. Secondary hypertension:

A patient is said to have secondary hypertension when a particular cause of hypertension can be found.

4.1.6. Risk factors[12]:

Risk factors of hypertension include age, gender, hereditary factors, race, overweight, increased salt and saturated fat intake, decreased intake

of dietary fiber, alcohol consumption, sedentary lifestyle, high socio-economic status and environmental stress.

4.1.7. Etiopathogenesis:

4.1.7. A. Genetic considerations[15]:

In rare Mendelian forms of hypertension lot of definite genetic variants have been found. These are applicable only to less than 2% of patients with essential hypertension. For many patients, hypertension is a polygenic disorder where in many genes act together with ecological factors; each gene has only a minimal role in causation of blood pressure.

Recent evidence proposes that genes that are components of the renin angiotensin aldosterone system (RAAS), together with ACE polymorphisms and angiotensinogen, may be associated with salt sensitivity of blood pressure and hypertension. Increased renal tubular reabsorption of sodium is believed to be related to the α-adducin gene; its variants may be related with blood pressure sensitivity to salt and hypertension. Other genes probably associated with hypertension are genes encoding the angiotensin II - type 1 (AT_1) receptor, aldosterone synthase and the β_2 receptor.[15]

4.1.7. B. Mechanisms of hypertension:

Intravascular volume[15]:

Vascular volume is a chief determining factor of blood pressure over the long term. Sodium is largely an extracellular ion and is a key determinant of the extracellular fluid volume. When intake of NaCl is more than the ability of

the renal system to excrete sodium, initially the vascular volume increases; this is followed by increase in cardiac output.

Increase in vascular volume causes increase in cardiac output which leads to the initial rise of blood pressure; in due course of time, the TPR increases and the cardiac output reverts back to normal. As high salt intake increases blood pressure, the kidney excretes more sodium; thus, the increase in arterial pressure maintains sodium balance. Decrease in absorbing capacity of the renal tubules, increase in the glomerular filtration rate (GFR) and hormonal factors such as atrial natriuretic factor are the causes for "pressure-natriuresis" phenomenon.

Autonomic nervous system[15]:

Cardiovascular homeostasis is maintained by autonomic nervous system (ANS) by pressure, volume and chemoreceptor signals. Short term regulation of blood pressure is by adrenergic reflexes; long term regulation of arterial pressure is by adrenergic function along with hormonal and volume related factors. The catecholamines, noradrenaline, adrenaline and dopamine (DA), play important roles in cardiovascular regulation.

Guanosine nucleotide binding regulatory proteins (G proteins) and intracellular concentrations of second messengers bring about the actions of the adrenergic receptors. Noradrenaline activates α receptors more than adrenaline and adrenaline activates β receptors more than noradrenaline. In smooth muscles α_1 receptors are present in postsynaptic cells; stimulation of these receptors brings about smooth muscle contraction. In postganglionic nerve terminals, α_2 receptors are located on presynaptic membranes;

stimulation of these receptors reduces the release of noradrenaline from the nerve terminals. Negative feedback of α_2 receptors comes into play when activated by catecholamines, thus preventing further noradrenaline release. Stimulation of myocardial β_1 receptors increases cardiac contraction and cardiac output; stimulation β_1 receptors on Juxtaglomerular cells increases renin release from the kidney. Vascular smooth muscle relaxation and vasodilation are brought about by activation of β_2 receptors by adrenaline.

Blood pressure is regulated by several reflexes, of which baroreceptor reflex is facilitated by sensory nerve endings, aortic branch of vagus nerve, carotid branch of glossopharyngeal nerve present in the aortic arch and the carotid sinuses; these nerve endings are sensitive to stretch. Increase in arterial pressure stimulates these nerve endings; this causes decrease in sympathetic outflow, leading to decrease in heart rate and blood pressure.

Renin angiotensin aldosterone system[15]:

The RAAS causes regulation of blood pressure by angiotensin II (Ang II) (which has vasoconstrictor property) and aldosterone (which has sodium retaining property). Renin is produced as an enzymatically inactive precursor, prorenin. There are three primary stimuli for renin secretion

i. Decrease in NaCl flux across the macula densa
ii. Decrease in pressure within the renal afferent arteriole
iii. Stimulation of renin secreting cells (Juxtaglomerular cells) by β_1 receptors

In the circulation, active renin converts angiotensinogen to inactive angiotensin I (Ang I). Angiotensin converting enzyme which is present

mainly on the luminal surface of pulmonary endothelial cells, converts Ang I to Ang II (active form). The same enzyme inactivates the vasodilator bradykinin. Ang II is a potent pressor substance that acts through AT_1 receptors on cell membranes. Ang II is also involved in the pathogenesis of atherosclerosis.

Vascular mechanisms[15]:

The key determinants of blood pressure are luminal size of resistance vessels (small arteries and arterioles) and elasticity of arteries. Even a small decrease in lumen size will greatly increase resistance. In hypertensive patients, the lumen size of small arteries and arterioles are reduced due to mechanical, structural or functional changes. Increased TPR occurs due to decrease in lumen size caused by hypertrophic or eutrophic vascular remodeling. Remodeling is also caused by low grade inflammation, apoptosis and vascular fibrosis. In a highly elastic vessel, even when the volume increases, there is only a little increase in pressure; in a semi rigid vessel, even with a small increase in volume, the pressure increases greatly.

Hypertensive patients have stiffer arteries and arteriosclerotic patients have decreased vascular compliance due to structural changes; this leads to high systolic blood pressures and wide pulse pressures. Hypertension related abnormalities of vascular growth and vascular tone is caused by ion transport by vascular smooth muscle cells, both of which are regulated by intracellular pH.

i. Na^+ dependent HCO_3^- Cl^- exchange
ii. Na^+ H^+ exchange

iii. Cation independent HCO_3^- Cl^- exchange

These ion channels participate in the regulation of intracellular pH.

Na^+ H^+ exchanger activity is increased in hypertension; this in turn causes increase in vascular tone either by increasing sodium entry which in turn leads to an increase in intracellular calcium or by increasing intracellular pH which leads to an increase in contractility for a given concentration of intracellular calcium. The vascular endothelium synthesizes and releases vasoactive substances like nitric oxide, a potent vasodilator which modulates vascular tone. This is impaired in hypertensive patients.

4.1.8. Clinical features[15]:

Most hypertensive patients will not have any specific symptoms. Headache is the commonest symptom seen in patients with severe hypertension; other symptoms include palpitations, dizziness, impotence and easy fatigability.

4.1.9. Pathologic consequences:

Heart[15]:

Heart disease is the most common cause of mortality in hypertensive individuals. It occurs due to functional and structural changes which causes left ventricular hypertrophy (LVH), coronary artery disease (CAD), chronic heart failure (CHF), cardiac arrhythmias and micro vascular disease. Patients with LVH have high possibility for CAD, CHF, CVA and unexpected death. CHF may be due to diastolic dysfunction or systolic dysfunction or

both. Diastolic function abnormalities are common in hypertensive patients; these may range from asymptomatic heart disease to heart failure.

Brain[15]:

CVA is the second common cause of mortality. CVA mainly occurs due to infarction, but may also occur due to subarachnoid or intracerebral hemorrhage. In elderly individuals the increase in systolic blood pressure increases the incidence of CVA.

Impaired cognition is seen in elderly hypertensive individuals. Due to auto regulation, blood flow to the brain remains constant over a wide range of arterial pressures. When this auto regulation fails, patients develop encephalopathy; and they present with headache, nausea, projectile vomiting, focal neurologic signs and altered mental status. If untreated, it may progress to seizures, stupor, coma and sudden death.

Kidney[15]:

Hypertension can lead to renal injury and end-stage renal disease. Renal risk is more with systolic arterial pressure and less with diastolic arterial pressure. Reliable marker for severity and progression of chronic kidney disease is proteinuria.

Preglomerular arterioles are affected in atherosclerotic hypertensive vascular disease of the kidney; this leads to ischemic alterations in glomerulus and post glomerular structures. Hyper perfusion of glomerulus occurs due to direct damage to the glomerular capillaries; this leads to glomerular injury. Auto regulation of renal blood flow and GFR fail with progression of renal injury: this leads to low blood pressure threshold for

renal damage. This causes further renal damage and nephron loss, which leads to severe hypertension and glomerular hyperfiltration. Glomerulosclerosis occurs and renal tubules become ischemic and atrophic. Fibrinoid necrosis of afferent arterioles are seen in malignant hypertension; it may extend to glomerulus and cause localized necrosis of glomerular tuft.

Peripheral arteries[15]:

Longstanding elevated blood pressure will lead to atherosclerotic changes in blood vessels. Increased risk of cardiovascular disease is seen in patients with arterial diseases of lower limb. The main symptom of peripheral arterial disease is intermittent claudication.

4.1.10. Diagnosis[14,15]:

Multiple automated ambulatory blood pressure readings recorded for 24 hours or more give accurate data than few readings taken in the clinic; they give better idea about target organ damage. Treatment should be given accordingly because ambulatory blood pressure readings are lower by 12/7 mm Hg than regular measurements. Treatment is decided based on average ambulatory daytime readings.

Diagnosis of hypertension is confirmed by a complete history and physical examination. Screening is done to find out any other cardiovascular risk factors, cardiovascular consequences of hypertension and secondary causes of hypertension.

Basic laboratory tests for initial evaluation:

i. Kidney: Microscopic urine analysis, urine albumin, renal function test

ii. Endocrine: Serum electrolytes and thyroid profile

iii. Metabolic: Blood glucose level and lipid profile

iv. Other: Haematology and electrocardiogram

4.1.11. Treatment:

Lifestyle interventions[15]:

Lifestyle changes help in prevention and treatment of hypertension**.** Hence, they are advised for individuals with prehypertension and for hypertensive individuals as an addition to drugs.

Lifestyle changes to manage hypertension[15]:

- Reduction of Weight with body mass index (BMI) < 25 kg/m^2
- Salt restricted diet < 6 g of NaCl/day
- Follow DASH (Dietary Approaches to Stop Hypertension) diet plan. Diet should include vegetables, fruits and products with reduced amount of fat
- Reduction of alcohol consumption
- Regular physical activity

Pharmacotherapy[15]:

Drug therapy is recommended for individuals with blood pressure ≥140/90 mmHg. Choice of antihypertensive agents and their combinations should depend on age, severity of hypertension, cardiovascular risk factors, comorbid conditions, cost, side effects and frequency of dosing. The antihypertensive drugs include α-blockers, β-blockers, CCBs (calcium channel blockers), diuretics, ACE inhibitors (Angiotensin converting enzyme

inhibitors), ARBs (Angiotensin receptor blockers) etc.; these are either used as monotherapy or as combination therapy.

4.2. Antihypertensive drugs:

4.2.1. Introduction[16]:

Lowering of blood pressure by antihypertensive drugs helps to prevent blood vessel damage and to reduce morbidity and mortality. Antihypertensive drugs acts by interfering normal arterial pressure regulation. Knowledge of mechanisms of antihypertensive drugs helps to predict their efficacy and toxicity resulting in rational use of these drugs.[16]

4.2.2. Classification of antihypertensive drugs[17]:

4.2.2.1. Diuretics:

i. Thiazides and related agents: Hydrochlorothiazide, chlorthalidone, chlorothiazide, indapamide, methylclothiazide and metolazone.
ii. Loop diuretics: Furosemide, torsemide, bumetanide, and ethacrynic acid.
iii. K^+ sparing diuretics: Spironolactone, amiloride and triamterene.

4.2.2.2. Sympatholytic drugs:

i. β-blockers: Metoprolol, betaxolol, nadolol, bisoprolol, esmolol, timolol, nebivolol, penbutolol, atenolol, pindolol and propranolol.
ii. α-blockers: Prazosin, terazosin, doxazosin, phenoxybenzamine and phentolamine.
iii. Mixed α and β receptor blockers: Labetalol and carvedilol.

iv. Centrally acting adrenergic agents: Methyldopa, clonidine, guanabenz and guanfacine.

v. Adrenergic neuron blocking agents: Guanadrel and reserpine.

4.2.2.3. Calcium channel blockers:

Verapamil, diltiazem, felodipine, nicardipine, isradipine, amlodipine and nifedipine.

4.2.2.4. Angiotensin converting enzyme inhibitors:

Captopril, ramipril, enalapril, lisinopril, quinapril, trandolapril, fosinopril, benazepril and perindopril.

4.2.2.5. Angiotensin receptor blockers:

Losartan, candesartan, irbesartan, valsartan, telmisartan, eprosartan and olmesartan.

4.2.2.6. Direct renin inhibitor:

Aliskiren

4.2.2.7. Vasodilators:

i. Arterial: Hydralazine, minoxidil, diazoxide and fenoldopam

ii. Arterial and venous: Nitroprusside

4.2.2.1. Diuretics:

i. Thiazides diuretics[16-18]:

Thiazides diuretics have antihypertensive effects when used alone; they enhance the efficacy of almost all other antihypertensive drugs.

Mechanism of action[16]:

Initially thiazides decrease extracellular volume by interacting with a thiazide sensitive NaCl co-transporter present in the distal convoluted tubule (DCT) in the kidney, enhancing Na^+ excretion in the urine, and leading to a fall in cardiac output. However, the hypotensive effect is maintained during long term therapy due to reduced TPR; cardiac output returns to pretreatment values and ECF volume returns almost to normal due to compensatory responses such as activation of RAAS.

Pharmacokinetics[17]:

All thiazides are administered orally as they are well absorbed by this route. Onset of action is less than 1 hour; duration of action varies from 6-48 hours. Most of the drugs undergo minimal metabolism in the liver and are excreted as such. They are filtered at the glomerulus; they are also secreted in the proximal tubule by organic anion transporter.

Adverse drug reactions[18]:

Central nervous system adverse effects include vertigo, headache, weakness, xanthopsia and paresthesias. Gastrointestinal adverse effects include nausea, vomiting, anorexia, constipation, cramping, diarrhea, cholecystitis and pancreatitis**.** Hematological disorders (e.g. blood dyscrasias)**,** dermatological disorders (e.g. photosensitivity and skin rashes) and erectile dysfunction also occur. Adverse effects related to fluid and electrolyte balance include extracellular volume depletion, hypotension, hyponatremia, hypokalemia, hypochloremia, hypomagnesemia, metabolic alkalosis, hyperuricemia and hypercalcemia. Glucose tolerance is impaired;

thus, latent diabetes mellitus may be unmasked during therapy. Thiazides also causes increase the plasma levels of triglycerides, low-density lipoprotein (LDL) cholesterol and total cholesterol.

Contraindications[18]:

Thiazide diuretics are contraindicated in individuals hypersensitive to sulfonamides.

Drug interactions[18]:

Thiazide diuretics decrease the effects of sulfonylureas, anticoagulants, insulin and uricosuric agents. They increase the effects of anesthetics, digitalis glycosides, diazoxide, loop diuretics, lithium and vitamin D. The effectiveness of thiazide diuretics may be reduced by nonsteroidal antiinflammatory drugs, nonselective or selective cyclooxygenase-2 (COX-2) inhibitors and bile acid sequestrants. Risk of thiazide induced hypokalemia is increased by amphotericin B and corticosteroids. A potentially lethal drug interaction is that involving thiazides and quinidine.Thiazides increase the risk of quinidine induced torsades de pointes.

Therapeutic uses[16]:

Thiazide diuretics are used for the treatment of renal, hepatic and cardiac oedemas, in hypertension (either alone or in combination with other antihypertensive drugs), calcium nephrolithiasis, osteoporosis, nephrogenic diabetes insipidus and bromide intoxication.

Dose[17]:

Thiazides are administered once daily. Common dose for hypertension is 25 mg/day of hydrochlorothiazide.

ii. Loop diuretic[17,18]:

Furosemide is the prototype drug of loop diuretics. It acts by inhibiting the Na^+ K^+ $2Cl^-$ symporter in the thick ascending limb of the loop of henle, and block its function, bringing salt transport in this segment of the nephron to a virtual standstill. Furosemide causes fall in blood pressure due to reduction of plasma volume and cardiac output. As the concentration of loop diuretic in the tubular lumen decreases, nephrons start to reabsorb Na^+, which often abolishes the whole effect of the loop diuretic on total body Na^+; this is called "postdiuretic Na^+ retention" phenomenon; it can be overcome by regular administration of the loop diuretics and salt restricted diet.

Pharmacokinetics[17,18]:

Furosemide is rapidly absorbed orally; bioavailability is about 60%. Lipid solubility is low; it is highly bound to plasma proteins. It is partly conjugated with glucuronic acid and mainly excreted unchanged by glomerular filtration as well as tubular secretion. Plasma $t_{1/2}$ is 1-2 hours.

Adverse effects[17,18]:

Adverse effects of loop diuretics are extracellular fluid volume depletion, hypokalemia, hypochloremic alkalosis, hyponatremia, hypomagnesemia, hypocalcemia and deleterious effects on bone metabolism. Loop diuretics also cause ototoxicity, hyperuricemia, hyperglycemia, increased plasma levels of triglycerides and LDL cholesterol and decreased plasma HDL (high density lipoprotein) cholesterol levels, photosensitivity, skin rashes, paresthesias, bone marrow depression and gastrointestinal upset.

Contraindications[17,18]:

Loop diuretics are contraindicated in severe volume and Na^+ depletion**,** patients sensitive to sulfonamides, anuria unresponsive to a test dose of loop diuretic and in postmenopausal osteopenic women.

Drug interactions[17,18]:

Drug interactions of loop diuretics are seen with aminoglycosides, carboplatin, paclitaxel, anticoagulants, digitalis glycosides, lithium, propranolol, sulfonylureas, cisplatin, NSAIDs, probenecid, thiazide diuretics and amphotericin B.

Therapeutic uses[17,18]:

Loop diuretics are used in the treatment of acute pulmonary oedema, CHF, hypertension, oedema of nephrotic syndrome, oedema and ascites of liver cirrhosis, in drug overdose to induce a forced diuresis, hypercalcemia, hyponatremia and oedema associated with chronic renal disease.

Dose[17,18]:

Furosemide is given 20-80 mg once daily in the morning. In renal insufficiency, up to 200 mg 6 hourly has been given by intramuscular or intravenous route; in pulmonary oedema, 40-80 mg may be given intravenously.

iii. Potassium sparing diuretics[17]:

Potassium sparing diuretics either antagonise aldosterone or directly inhibit Na^+ channels in DCT and collecting duct cells to indirectly conserve K^+.

A. Spironolactone (Aldosterone antagonist)[17]:

Spironolactone acts from the interstitial side of the tubular cell, attaches with the mineralocorticoid receptor and prevents the formation of aldosterone-induced proteins (AlPs) in a competitive manner. It has no effect on Na^+ and K^+ transport in the absence of aldosterone, while under normal circumstances, it increases Na^+ and decreases K^+ excretion. Spironolactone is a mild saluretic because majority of Na^+ has already been reabsorbed proximal to its site of action. However, it antagonises K^+ loss induced by other diuretics and slightly adds to their natriuretic effect.

Pharmacokinetics[17]:

The oral bioavailability of spironolactone is 75%. It is highly plasma protein bound; it undergoes complete metabolism in liver. The $t_{1/2}$ of spironolactone is 1-2 hours and the $t_{1/2}$ of its active metabolite canrenone is 18 hours.

Dose[17]: 25-50 mg twice to four times per day.

Use[17]:

Spironolactone is used in oedema and to counteract K^+ loss due to thiazide and loop diuretics. It is also used in hypertension only as adjuvant to thiazides to prevent hypokalaemia. It is also used in moderate to severe CHF as an additional drug to conventional therapy.

Drug interactions[17]:

Drug interactions of spironolactone are seen with K^+ supplements, aspirin, ACE inhibitors, ARBs and digoxin.

Adverse effects[17]:

Adverse effects of spironolactone are drowsiness, confusion, abdominal upset, hirsutism, gynaecomastia, impotence, menstrual irregularities, hyperkalaemia, acidosis and aggravation of peptic ulcer.

B. Inhibitors of renal epithelial Na^+ channel[17,18]:

Triamterene and amiloride are two inhibitors of renal epithelial Na^+ channel with identical actions.

Mechanism of action[17,18]:

The luminal membrane of late DCT and collecting duct cells expresses a distinct 'amiloride sensitive' or 'renal epithelial' Na^+ channel, through which Na^+ enters the cell down its electrochemical gradient, which is generated by Na^+ K^+ ATPase operating at the basolateral membrane. This Na^+ entry partially depolarizes the luminal membrane, creating a transepithelial potential difference which promotes K^+ secretion into the lumen through K^+ channels. Though there is no direct coupling between Na^+ and K^+ channels, the more the delivery of Na^+ to the distal nephron, the greater is its entry through the Na^+ channel, the greater is the extent of depolarization of the luminal membrane, the greater is the driving force for K^+ excretion.

Pharmacokinetics[17,18]:

Triamterene is incompletely absorbed orally, partly bound to plasma proteins, largely undergoes hepatic metabolism and excreted in urine. Plasma $t_{1/2}$ is 4 hours; the effect of a dose lasts for 6-8 hours.

Adverse effects[17,18]:

Nausea, dizziness, muscle cramps, rise in blood urea, impaired glucose tolerance and photosensitivity.

Use[17,18]: Triamterene is used in treatment of hypertension and oedema.

Dose[17,18]: 50-100 mg daily

4.2.2.2. Sympatholytic drugs:

i. Beta blockers[17,18]:

Adrenergic responses brought by β receptors are inhibited by β blockers. All β blockers act as competitive antagonists. It is also an inverse agonist.

Mechanism of action[17,18]:

Propranolol acts by blocking β_1 and β_2 receptors; it weakly blocks β_3 receptor. Propranolol blocks vasodilatation and fall in blood pressure caused by isoprenaline and increases the rise in blood pressure caused by adrenaline. Vasomotor reversal (seen after α-blockade) is re-reversed. Only a small change in blood pressure is brought by its direct action on blood vessels. On long term administration blood pressure gradually falls in hypertensives but not in normotensives. Initially total peripheral resistance (TPR) is increased and cardiac output is reduced, so that there is only a small change in blood pressure. On long term administration, resistance vessels gradually adapt to chronically reduced cardiac output so that TPR falls; hence, both systolic and diastolic blood pressure fall. Other mechanisms involved are:

i. Decreased noradrenaline release from sympathetic terminals due to blockade of β_2 receptors on presynaptic membrane.

ii. Reduced renin release from renal system (β_1 mediated): Propranolol causes a more marked fall in blood pressure in patients with normal or high plasma renin levels and these patients respond at comparatively lower doses than those with low levels of plasma renin.

iii. Central action reducing sympathetic outflow.

Pharmacokinetics[17,18]:

On oral administration, propranolol is well absorbed, but bioavailability is low due to high first pass metabolism in liver. It is lipophilic and penetrates into brain easily. Metabolism of propranolol is dependent on blood flow to the liver. Bioavailability can be increased by taking it with meals because food decreases its first pass metabolism. More than 90% of propranolol is plasma protein bound. The metabolites are excreted in urine, mostly as glucuronides.

Dose[17,18]:

10 mg twice daily to 160 mg 6th hourly given orally, intravenously: 2 to 5 mg injected over 10 min.

Drug interactions[17,18]:

Drug interactions of propranolol are seen with digitalis, verapamil**,** insulin and oral antidiabetic drugs, phenylephrine, ephedrine, indomethacin, cimetidine, lidocaine and chlorpromazine.

Adverse effects and contraindications[17,18]:

Adverse effects of propranolol are bradycardia, worsening of chronic obstructive pulmonary disease (COPD), exacerbation of variant angina, impairment of carbohydrate tolerance in prediabetics, increase of total triglycerides and LDL cholesterol and reduction of HDL cholesterol, tiredness, reduced exercise capacity , deterioration of peripheral vascular disease, cold extremities, gastrointestinal upset, lack of drive, nightmares, forgetfulness, hallucinations and sexual distress. Withdrawal of propranolol after chronic use should be gradual as it may cause rebound hypertension, deterioration of angina and even sudden death. Propranolol is contraindicated in myocardial insufficiency, asthmatics and in partial and complete heart block.

ii. α_1 Adrenergic receptor antagonists[17,18]:

The drugs that blocks only α_1 receptors without blocking α_2 receptors form one more group of antihypertensive drugs. Prazosin, terazosin, and doxazosin are the agents that are available for the treatment of hypertension.

Mechanism of action[17,18]:

α_1 adrenergic receptor antagonists are selective α_1 blockers. All subtypes of α_1 receptor ($\alpha_{1A,}$ $\alpha_{1B,}$ α_{1D}) are blocked in the same way; this brings about vasodilation and fall in blood pressure.

Initially α_1 receptor blockers decrease TPR and increase venous capacitance; this causes a reflex increase in heart rate and plasma renin activity. On long term treatment, only vasodilation persists; heart rate,

cardiac output and plasma renin activity return to normal. On long term therapy, salt and water retention occurs in many people; this attenuates the postural hypotension.

Adverse Effects[17,18]:

The α_1 adrenergic blockers cause postural hypotension, nasal blockade, headache, weakness, drowsiness, dry mouth, palpitation, rash, blurred vision and impaired ejaculation in males.

Therapeutic Uses[17,18]:

α_1 receptor blockers are not used as monotherapy for hypertensives; are used mostly in combination with β blockers, diuretics and other antihypertensive drugs. α_1 receptor blockers are good drugs for hypertensive patients with BPH, because they also improve urinary symptoms. Prazosin improves carbohydrate metabolism, lowers LDL cholesterol and triglycerides and increases HDL.

Pharmacokinetics[17,18]:

Prazosin is orally effective (bioavailability is 60%), highly plasma protein bound, undergoes hepatic metabolism and excreted mainly in bile. Its plasma $t_{1/2}$ is 2-3 hours; the effect of a dose lasts for 6-8 hours.

Dose[17,18]:

Initially prazosin is started at low dose (0.5 mg) given at bedtime and slowly increased to twice daily therapy till a sufficient response is produced (maximum dose of 10 mg twice daily).

iii. Mixed α and β Adrenergic blockers:

Labetalol[18]:

Labetalol blocks both α and β receptors. It blocks $\beta_1 + \beta_2 + \alpha_1$; it also has weak β_2 agonistic activity. It blocks β receptors 5 times more potently than α. Labetalol at low doses has effects like those of propranolol alone, but at high doses has effects that are like a combination of prazosin and propranolol. Fall in blood pressure (both systolic and diastolic) is due to blockade of α_1 and β_1 and β_2 agonistic activity. At high doses it reduces both TPR and cardiac output. On the contrary to propranolol, labetalol increases blood flow to the limbs. In adrenergic nerve endings it inhibits noradrenaline uptake by the nerve endings. Labetalol is effective orally but undergoes high first pass metabolism. It is only a moderately potent antihypertensive and is useful in clonidine withdrawal and pheochromocytoma.

Adverse reactions are rashes, postural hypotension, failure of ejaculation and liver damage.

Dose: Initially start with 50 mg twice daily, escalate to 100-200 mg thrice daily orally. 20-40 mg intravenously every 10 min (until desired response) is given in hypertensive emergencies.

Carvedilol[17,18]:

Carvedilol is a $\beta_1 + \beta_2 + \alpha_1$ blocker; it produces vasodilatation due to α_1 blockade and calcium channel blockade, but it lacks intrinsic sympathomimetic activity; it also has antioxidant property. It is used in hypertension; is the β blocker used in CHF as cardioprotective. Carvedilol combined with usual therapy reduces mortality and reduces MI.

Pharmacokinetics[17,18]:

On oral administration, carvedilol is well absorbed; peak plasma levels are attained at 1-2 hours. It is highly lipophilic and thus, is extensively distributed into extravascular tissues. It is > 95% protein bound and is extensively metabolized in the liver. The $t_{1/2}$ is 7-10 hours.

Drug interactions[17,18]:

Carvedilol undergoes extensive oxidative metabolism in the liver; its pharmacokinetics can be markedly affected by drugs that inhibit or induce oxidation. These include the inducer rifampicin and inhibitors such as cimetidine, quinidine, fluoxetine and paroxetine.

Uses[17,18]:

Carvedilol is used in hypertension, CHF and left ventricular dysfunction following MI.

- CHF: Start with 3.125 mg twice daily for 2 weeks; if well tolerated gradually increase to a maximum of 25 mg twice daily.
- Hypertension/angina: Start with 6.25 mg twice daily; gradually increase to a maximum of 25 mg twice daily.

iv. Central sympatholytics:

Clonidine[18]:

Clonidine is an imidazoline derivative having complex actions. Clonidine is a partial agonist with high affinity and high intrinsic activity at α_2 receptors, especially α_{2A} subtype in brainstem. The major hemodynamic effects result from stimulation of α_{2A} receptors present mainly postjunctionally in

vasomotor centre of medulla; this decreases sympathetic out flow, resulting in fall in blood pressure and bradycardia. Plasma noradrenaline also declines. Clonidine is a moderately potent antihypertensive. Presence of imidazoline receptors (which are distinct from α_2 receptors) has now been confirmed in the brain as well as periphery. These are activated by clonidine and related drugs but not by noradrenaline. Clonidine may stimulate central imidazoline receptors; these receptors then stimulate medullary α_{2A} receptors to reduce sympathetic outflow. Clonidine also appears to directly stimulate α_{2A} receptors (producing hypotension as well as sedation). Rilmenidine and moxonidine are selective cerebral imidazoline receptor agonists with low α_{2A} receptor affinity. Therefore, they have low sedative property but equivalent antihypertensive action.

Rapid intravenous injection of clonidine raises blood pressure transiently due to activation of peripheral postsynaptic vasoconstrictor α_{2B} receptors at the high concentrations so attained. Oral doses producing lower plasma clonidine levels cause only fall in blood pressure, because clonidine has lower intrinsic activity on α_{2B} receptors which predominate in vascular smooth muscle. Probably for the same reason, clonidine exhibits the therapeutic window phenomenon: optimum lowering of blood pressure occurs between blood levels of 0.2-2.0 ng/ml. At higher concentrations, fall in blood pressure is less marked. On chronic administration of clonidine, decrease in cardiac output contributes more to the fall in blood pressure than decrease in TPR. Decreased sympathetic flow to the kidney results in reduced renin release.

Pharmacokinetics[18]:

On oral administration clonidine is well absorbed; it attains peak plasma levels in 2-4 hours; 1/2 to 2/3 of an oral dose is excreted unchanged in urine, the rest as metabolites. Plasma $t_{1/2}$ is 8-12 hours. Effect of a dose lasts for 6-24 hours.

Dose[18]:

100 µg once or twice daily, maximum 300 µg thrice daily, orally or intramuscularly.

Adverse effects[18]:

Adverse effects of clonidine are sedation, mental depression, disturbed sleep, dryness of mouth, nose and eyes, constipation, impotence, salt and water retention, bradycardia and postural hypotension. Alarming rise in blood pressure, in excess of pretreatment level, with tachycardia, restlessness, anxiety, sweating, headache, nausea and vomiting occur in some patients when doses of clonidine are missed for 1-2 days. This is due to:

- Sudden removal of central sympathetic inhibition resulting in release of large quantities of stored catecholamines.
- Supersensitivity of peripheral adrenergic structures to catecholamines that develops due to chronic reduction of sympathetic tone during clonidine therapy.

A combination of α blocker with a β blocker or a potent vasodilator or clonidine itself can be used to treat the syndrome.

Interactions[18]:

Tricyclic antidepressants and chlorpromazine abolish the antihypertensive action of clonidine by blocking α-receptors on which clonidine acts.

Use[18]:

Clonidine is occasionally used in treatment of hypertension (in combination with a diuretic) and for opioid withdrawal, alcohol withdrawal and smoking cessation. It has been used to substitute morphine for intrathecal/epidural surgical and postoperative analgesia. When administered preoperatively, it diminishes anaesthetic requirement. Clonidine attenuates vasomotor symptoms of menopausal syndrome. It has been used to control loose motions due to diabetic neuropathy; it is used in the clonidine suppression test for pheochromocytoma.

V. Adrenergic neuron blockers:

Reserpine[18]:

Reserpine is an alkaloid obtained from the roots of Rauwolfia serpentina. It has been used in 'Ayurvedic' medicine for centuries. In 1955 the pure alkaloid was isolated; later, it was found to act by causing depletion of catecholamines and 5-hydroxytryptamine. In late 1950s and early 1960s, it was a popular antihypertensive drug; but at present, it is used only as a pharmacological tool. Monoamines are stored in intra neuronal vesicles. Reserpine acts by irreversibly inhibiting the vesicular monoamine transporter (VMAT2) located on the membrane of these vesicles; therefore, the monoamines are not taken up by the vesicles. In the cytoplasm, they are

metabolized by monoamine oxidase (MAO); the net result is depletion of monoamines from storage vesicles. Even after drug is eliminated, the effects last for a long time; hence, it is called “hit and run drug”; this is because tissue catecholamine stores are restored only gradually. At higher doses, it depletes catecholamines and 5-hydroxytryptamine in the brain as well; this causes sedation and mental depression.

4.2.2.3. Calcium channel blockers[18]:

Important classes of CCBs include phenyl alkylamines (e.g. verapamil)**,** dihydropyridines (e.g. nifedipine) and benzothiazepines (e.g. diltiazem). All the three classes are equally efficacious antihypertensive drugs.

Calcium channels[18]:

In smooth muscles (other excitable cells as well), three types of Ca^{2+} channels are seen

a) Voltage sensitive channels (three major types include L-type, T-type and N-type channels)
b) Receptor operated channels
c) Leak channels

L-type calcium channels are composed of a major α_1 subunit and other modulatory subunits like α_2, β, γ and δ. Each subunit has multiple isoforms; these isoforms may be site specific. CCBs block only the L-type channels. The three classes of CCBs bind to their own specific binding sites on the α_1 subunit; by doing so restrict Ca^{2+} entry. Also, different drugs have different affinities for various isoforms of L-type channels. In cardiac or smooth muscle cell, CCBs inhibit Ca^{2+} mediated slow channel part of action potential

(AP), causing negative inotropic, chronotropic, and dromotropic effects and relaxation of smooth muscle. Of the three classes of CCBs the DHPs have the most marked smooth muscle relaxant and vasodilator action; this is because they have additional effects such as inhibition of cAMP-phosphodiesterase (which increases cAMP in smooth muscle).

Nifedipine[18]:

Nifedipine is the prototype DHP, it has rapid onset and short duration of action. The principal action of nifedipine is dilatation of arterioles; hence, TPR reduces and blood pressure falls. At much higher doses, it has a direct depressant effect on heart. It does not affect A-V or SA node conduction. Reflex sympathetic stimulation of heart predominates leading to increased heart rate, myocardial contractility and cardiac output. Increased coronary flow is seen.

Dose[18]:

5-20 mg twice daily to thrice daily orally.

Adverse effects[18]:

Hypotension, palpitation, flushing, ankle oedema, headache, drowsiness and nausea; frequency of angina is increased; among post MI patients mortality is higher; increased urine voiding difficulty in elderly males; and hindrance to diabetes control (due to reduction of insulin release).

Pharmacokinetics[18]:

All CCBs are well absorbed orally; they attain peak at 1 to 3 hours (except for amlodipine which attains peak level at 6 to 9 hours). Due to high

first pass metabolism, oral bioavailability is incomplete with striking individual variations. All are highly plasma protein bound. The CCBs have extensive tissue distribution and high clearance. All undergo hepatic metabolism and are excreted in urine. The elimination $t_{1/2}$ are in the range of 2 to 6 hours (but the elimination $t_{1/2}$ of amlodipine is exceptionally long).

Uses[18]:

CCBs are used in angina pectoris, hypertension and cardiac arrhythmias. Nifedipine is used as an alternative drug for premature labour; verapamil is used to suppress nocturnal leg cramps; DHPs decrease severity of Raynaud's episodes.

4.2.2.4. Angiotensin converting enzyme (ACE) inhibitors[17,18]:

Mechanism of Action[17,18]:

Decreased sodium flux across macula densa, decreased renal arterial pressure and sympathetic stimulation cause release of renin from the juxtaglomerular apparatus. Renin converts angiotensinogen to inactive angiotensin I (Ang I). ACE which is present mainly on luminal surface of pulmonary endothelial cells, converts Ang I to Ang II (active form), which has sodium retaining and vasoconstrictor activities. Ang II is converted to angiotensin III by aminopeptidase A. Angiotensin II and III stimulate aldosterone secretion by zona glomerulosa.

ACE inhibitors prevent the generation of the active principle, angiotensin II. In patients with essential hypertension, it has been found that RAAS is overactive in 20%, normal in 60% and hypoactive in the rest. Thus, it contributes to the maintenance of vascular tone in over 80% of cases; in

these cases its inhibition results in lowering of blood pressure. In normotensive, Na^+ replete individuals, the fall in blood pressure attending the initial few doses of ACE inhibitors is modest. This is more marked when Na^+ has been depleted by dietary restriction or diuretics. A greater fall in blood pressure occurs in renovascular, accelerated and malignant hypertension.

Pharmacokinetics[17,18]:

Nearly 70% of orally administered captopril is absorbed. If taken with food its bioavailability is decreased. It is partly metabolized and partly excreted unchanged in urine. The plasma $t_{1/2}$ is 2 hours, but actions last for 6 to 12 hours.

Adverse effects[17,18]:

The adverse effects of ACE inhibitors include hypotension, hyperkalemia, cough, rashes, urticaria, angioedema, dysgeusia, headache, dizziness, nausea, bowel upset, granulocytopenia and proteinuria. Fetal growth retardation, organ hypoplasia and fetal death may occur if given during the later half of pregnancy.

Contraindications[17,18]:

ACE inhibitors are contraindicated in patients with bilateral renal artery stenosis as they precipitate acute renal failure in these patients.

Drug interactions[17,18]:

Indomethacin and other NSAIDs attenuate the hypotensive action. Incidents of renal failure have been reported when a NSAID was given to

patients receiving ACE inhibitor with diuretic. Hyperkalemia can occur if K^+ supplements/K^+ sparing diuretics are given with captopril. Antacids reduce bioavailability of captopril: ACE inhibitors reduce lithium clearance and predispose to its toxicity.

Dose[17,18]:

25 mg twice daily, increased gradually upto 50 mg thrice daily according to response. In patients on diuretics and in CHF patients it is wise to start with 6.25 mg twice daily to avoid marked fall in blood pressure initially. Tablets are taken one hour before or two hours after a meal.

Uses[17,18]:

ACE inhibitors are used in hypertension, CHF, MI, prophylaxis in high cardiovascular risk subjects, diabetic nephropathy and scleroderma crisis.

4.2.2.5. Angiotensin receptor blockers[18]:

AT_1 receptor blockers include losartan, candesartan, valsartan, telmisartan and irbesartan. Selective antagonists of AT_2 receptors, as well as combined AT_1 + AT_2 antagonists have also been produced.

Losartan[18]:

Losartan is competitive antagonist and inverse agonist of angiotensin II. It is more selective for AT_1 than for AT_2 receptor; it does not have action on any other ion channel or receptor, except thromboxane A_2 receptor. It blocks all overt actions of angiotensin II, namely vasoconstriction, central and peripheral sympathetic stimulation, release of aldosterone and adrenaline from adrenals, renal actions promoting salt and water reabsorption, central

actions like thirst, vasopressin release and growth promoting actions on heart and blood vessels. Losartan causes fall in blood pressure in hypertensive patients which lasts for 24 hours, while heart rate remains unchanged and cardiovascular reflexes are not interfered.

Pharmacokinetics[18]:

Food does not interfere with oral absorption of losartan; however, bioavailability is only 33% due to high first pass metabolism. It is partly carboxylated in liver to E3174; this active metabolite is a more potent noncompetitive AT_1 receptor antagonist. After oral ingestion, peak plasma levels are attained at 1 hour for losartan and at 3 to 4 hours for E3174. Both compounds are 98% bound to plasma protein, do not cross blood brain barrier and are excreted by the kidney. The plasma $t_{1/2}$ of losartan is 2 hours, but that of E3174 is 6 to 9 hours. No dose adjustment is required in renal insufficiency, but the dose should be reduced in presence of liver dysfunction.

Adverse effects[18]:

Losartan is well tolerated. But it can cause hypotension, hyperkalemia, dry cough, angioedema, headache, dizziness, weakness and upper gastrointestinal side effects. It has fetopathic potential; it should be avoided during pregnancy.

Dose[18]:

50 mg once daily; in liver disease or volume depletion, the dose is 25 mg once daily; addition of hydrochlorothiazide 12.5-25 mg enhances its effectiveness.

Uses[18]:

Used in hypertension, CHF, MI and diabetic nephropathy.

4.2.2.6. Direct Renin Inhibitors[17]:

Like ACE inhibitors and ARBs, direct renin inhibitors are drugs that inhibit the renin angiotensin pathway; they have efficacy in the treatment of cardiovascular disease. Aliskiren is a direct renin inhibitor; it interrupts this pathway by inhibiting the capacity of renin to produce angiotensin I from angiotensinogen.

Aliskiren has been used as an add-on drug in patients with hypertension, rather than as a replacement for other successful therapies.

Mechanism of Action[17]:

The initial renin inhibitors were peptide analogues of sequences either in renin itself or included the renin cleavage site in angiotensinogen. While effective in inhibiting renin and lowering blood pressure, these peptide analogues were effective only parenterally. However, aliskiren is effective following oral administration; it directly and competitively inhibits the catalytic activity of renin.

Pharmacological Effects[17]:

Aliskiren's inhibition of renin leads to diminished production of Ang I and ultimately Ang II and aldosterone with a resulting fall in blood pressure. Aliskiren along with ACE inhibitors and AT_1 receptor antagonists leads to an adaptive increase in the plasma concentrations of renin; but as aliskiren

inhibits renin activity, plasma renin activity does not increase as occurs with these other classes of drugs.

Absorption, Metabolism, and Excretion[17]:

Aliskiren is poorly absorbed, with a bioavailability of < 3%. Taking the drug with a high-fat meal may substantially decrease plasma concentrations. Aliskiren has an elimination $t_{1/2}$ of at least 24 hours. Elimination of the drug may be primarily through hepatobiliary excretion with limited metabolism via CYP3A4.

Toxicity and Precautions[17]:

Aliskiren is generally well tolerated. ADRs includes diarrhoea, cough and angioedema. Drugs acting on the RAAS may damage the fetus and should not be used in pregnant women.

Therapeutic Uses[17]:

Aliskiren is effective as monotherapy in treating patients with hypertension with dose dependent increasing efficacy at 150 to 300 mg/day. The combination of aliskiren with hydrochlorothiazide has a greater lowering effect on blood pressure than either drug alone. Aliskiren also appears to have greater efficacy when added to other agents in the treatment of hypertension including ACE inhibitors, ARBs and CCBs. Overall, aliskiren appears to be an effective antihypertensive drug that is well tolerated.

4.2.2.7. Vasodilators:

i. Arterial vasodilators[18]:

Hydralazine dilates resistance vessels; it has little action on capacitance vessels. Therefore, it reduces TPR. It reduces diastolic blood pressure more than systolic blood pressure. This causes reflex compensatory changes, such as increase in heart rate, increase in cardiac output and renin release; this in turn increases aldosterone, which causes retention of Na^+ and water. This disproportionate cardiac stimulation indicates that other actions, such as direct increase in noradrenaline release and myocardial contractility, are also involved. Despite the fall in blood pressure, renal blood flow is not decreased; but retention of fluid and oedema may occur. If β blockers or diuretics are not given with hydralazine, tolerance develops to its hypotensive action.

Pharmacokinetics[18]:

Hydralazine is well absorbed orally. It undergoes first pass metabolism in the liver; the main pathway is acetylation. There are fast acetylators (30-40% of Indians) as well as slow acetylators (60-70% of Indians). Slow acetylators have higher bioavailability. Hydralazine undergoes complete metabolism both in liver and plasma; the metabolites are excreted in urine. $t_{1/2}$ is 1-2 hours; but the hypotensive effect lasts longer.

Dose[18]:

25-50 mg once to thrice daily.

Adverse drug reactions[18]:

ADRs are conjunctival congestion, nasal stuffiness, facial flushing, headache, dizziness, palpitation, fluid retention, oedema and CHF. It may precipitate MI and angina in patients with CAD. Other ADRs are paresthesias, tremors and muscle cramps. Lupus syndrome develops with prolonged use of doses above 100 mg/day. Slow acetylators are more prone to develop this syndrome.

Uses[18]:

Hydralazine is used in hypertension uncontrolled by first line antihypertensive drugs. It is used only in combination with a diuretic and / or β blockers. It is one of the preferred antihypertensive drugs in pregnant women with pre-eclampsia. It is occasionally used in hypertensive emergencies. It can be used in the management of CHF (in combination with isosorbide dinitrate).

Contraindications[18]: In elderly and in patients with ischemic heart disease.

ii. Arterial and venous vasodilators:

Sodium nitroprusside[18]:

Sodium nitroprusside is a vasodilator; the onset of action is rapid; the duration of action is short. It is administered intravenously as infusion. By adjusting the rate of intravenous infusion, the vascular tone can be adjusted. It is both an arteriolar and a venous dilator; therefore, it that decreases both TPR and venous return. Myocardial workload is decreased; ischemia risk is not accentuated. It increases plasma renin activity. In patients with CHF and

ventricular dilatation, nitroprusside reduces afterload and preload and thus, improves ventricular function and cardiac output. In RBC's and endothelial cells, nitroprusside is split to release nitrous oxide both enzymatically and non-enzymatically; nitrous oxide relaxes vascular smooth muscle. This is the reason for the vasodilator action of nitroprusside.

In 500 ml of glucose/ saline solution, 50 mg of nitroprusside is added. The infusion is started at 0.02 mg/min and titrated upward the response; 0.1-0.3 mg/ min is often needed. The infusion bottle is covered with black paper; this is because it decomposes on exposure to light. Nitroprusside is converted in erythrocytes to cyanide; cyanide is converted in liver to thiocyanate, which is excreted slowly. Infusion of larger doses for 1-2 days may cause thiocyanate accumulation; this occurs particularly in patients with renal insufficiency; thiocyanate toxicity manifests as psychosis, disorientation and convulsions.

Side effects[18]:

Excessive sweating, palpitation, nervousness, vomiting, abdominal pain, weakness, disorientation and lactic acidosis.

4.3. Drug utilization studies:

4.3.1. Introduction[19]:

Drug utilization studies are dominant investigative kit to learn the function of drugs in society. They generate a thorough socio-medical and strong economic base for making healthcare decision.

4.3.2. Definition[20]:

According to WHO drug utilization is defined as "the marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences".

4.3.3. Objectives[21]:

The principal objective of DUS is to facilitate rational use of drugs in the population.

1. To increase our understanding of how drugs are being used.
2. To give an early signal of irrational use of a drug
3. To analyse whether the steps taken to improve drug utility have had the required impact.
4. To help the healthcare system to know, interpret, analyse and improve the drug prescription, use and administration of medication.
5. To provide insight into the effectiveness of drug use.
6. To set priority for sensible distribution of healthcare budgets

4.3.4. Types of drug use information[20]:

In DUS the following drug use information are essential

1. Drug based information
2. Problem based information
3. Patient information
4. Prescriber information

4.3.5. Drug utilization methods[22]:

1. Methods used in qualitative studies

2. Studies on prescription habits
3. Studies on patient compliance
4. Studies on drug effects
5. Studies on patients awareness about drugs
6. Consumption studies
7. Descriptive studies, effect of drug use and determinants of drug utilization

4.3.6. Sources of drug utilization data[20]:

Data can be obtained from general practitioners, from pharmacy records, from drug regulatory agencies, from drug suppliers and straight from population through health surveys like surveys conducted among females, elderly out patients or at national level.

4.3.7. Study designs for drug utilization studies[20]:

The study designs in DUS are

- Prospective
- Concurrent
- Retrospective

Prospective DUS involves evaluating the patient's disease and its intended drug therapy before a drug is given. It generally addresses generic substitution, drug-disease contraindications, therapeutic interchange and wrong dosage, improper duration of treatment, clinical abuse and drug allergy.

Concurrent DUS involves monitoring of drug therapy which is on progress, to guarantee positive results. It addresses drug - age precautions, extreme dose, low or high dosage, over or underutilization, drug-drug interactions.

Retrospective DUS involves review of drug therapy after the patient has taken the drug. It may notice the prescribing pattern of the drugs, administering or dispensing drugs to avoid improper use of drugs. It includes case report, case series and case control studies.

4.3.8. WHO drug use indicators[20]:

4.3.8.A. Core indicators:

a) Prescribing indicators:
   - Average number of medications per consultation
   - Percentage of medications prescribed by generic name
   - Percentage of medications prescribed from essential drug list
   - Percentage of consultations with injections
   - Percentage of consultations with antibiotics

b) Patient care indicators:
   - Average consultation time
   - Average dispensing time
   - Patient's awareness about correct dosage
   - Percentage of drugs actually dispensed

c) Facility indicators:
   - Availability of copy of EDL
   - Availability of important drugs

4.3.8.B. Complementary indicators:

- Percentage of patients treated without medications
- Average drug cost per consultation
- Percentage of drug cost spent on injections

4.3.9. Steps in drug utilization studies[23]:

- Recognize therapeutic areas of practice or drugs to include in the program
- Design of study
- Define criteria and standards
- Design the data collection form
- Data collection
- Evaluate results
- Provide feedback of results
- Develop and implement interventions
- Reassess and revise the drug utilization evaluation program

4.4. Pharmacovigilance:

4.4.1. Introduction[24,25]:

In the recent trend, people are using more efficient and newer drugs for diverse medical conditions in large scale; these drugs are being produced with developing scientific advances. The two important concerns about any drug are efficacy and safety. The pharmacovigilance plays a vital role in rational use of drugs by giving details about the ADRs shown by the drugs in the general population.

4.4.2. Definition[24]:

WHO defined the Pharmacovigilance as the pharmacological science relating to the detection, evaluation, understanding and prevention of adverse effects, particularly long term and short term side effects of medicines.

4.4.3. Objectives of phrmacovigilance[25]:

- Expand precaution for patient.
- Increase public protection from the new products.
- To contribute the knowledge of value, detriment, efficiency and hazard of medicines.
- Encourage edification and clinical training.
- Endorse healthy communication to the community.
- To promote rational and safe use of medicines.

4.4.4. Current status of Pharmacovigilance in India[24-28]:

In the world, India stands fourth among producers of pharmaceuticals. It is rising as one of the clinical trial hub in the world. Our country introduces many new drugs and hence there is a need for an energetic pharmacovigilance system in the country to guard the people from the possible harm that may be caused by some of these new drugs. Evidently conscious about the extent of the task, the Central Drugs Standard Control Organization (CDSCO) has started a well planned and highly participative National Pharmacovigilance Program. It is mainly based on the recommendations made in the WHO document titled “Safety Monitoring of Medicinal Products Guidelines for Setting up and Running a

Pharmacovigilance Centre". Pharmacovigilance has not come up well in India and the subject is in its early stage. The rate of pharmacovigilance in India is less than 1% when compared with the world rate of 5%. This is because of lack of knowledge about the subject and also deficiency in training. Now a days in India, pharmacovigilance situation has been progressing step by step than what it was in the past.

4.5. Pharmacoeconomics[18,29]:

Pharmacoeconomics is the science of assigning costs and outcomes of drug therapy. Pharmacoeconomics includes the identification, measurement and comparison of the costs, risks, results and benefits of programmes, services or individual therapies. Its aim is to compare the alternative solutions available on the basis of the relationship between necessary resources and results to be obtained. This definition highlights two concepts of fundamental importance for application of the economic principle the possibility of choosing between alternatives and comparing on the basis of costs and effects.

There are four types of pharmacoeconomic evaluations:

1. Cost minimization analysis (CMA): It involves comparing two or more treatment alternatives with the same outcome to determine the least costly alternative.
2. Cost effectiveness analysis (CEA): It compares programme or treatment alternatives with different safety and efficacy profiles.

3. Cost utility analysis (CUA): It captures the impact of a therapy on the quality of life. It provides a method for estimating patient preference for a particular intervention in terms of the patient's wellbeing.
4. Cost benefit analysis (CBA): It allows the identification, measurement and comparison of the benefits and costs of programme/treatment alternatives by comparing the benefits from the treatment alternative with the costs of providing the same.

4.6. Studies related to Drug utilization pattern of antihypertensive drugs:

A DUS of antihypertensive agents in essential hypertension done in Kathmandu, Nepal by Joshi et al.[4] showed that CCBs are most commonly used followed by β-blockers, diuretics, ACE inhibitors and ARBs. Among two drug combinations, most commonly used combination was amlodipine with atenolol followed by amlodipine with diuretic, amlodipine with enalapril, atenolol with diuretic, atenolol with enalapril and atenolol with losartan. The highest prescribed combination of three drugs is amlodipine with atenolol and enalapril followed by the combination of amlodipine with atenolol and losartan.

A DUS of antihypertensive drugs done in Karolinska Institute, Huddinge, Sweden by Al-Windi et al.[6] showed that β-blockers were most commonly used drugs followed by diuretics, ACE inhibitors and CCBs.

A DUS of antihypertensive drugs done in 20 private hospitals of Tanzania by Rimoy et al.[7] showed that most frequently prescribed antihypertensive drug as monotherapy was atenolol followed by bendrofluazide, frusemide, hydralazine, nifedipine, amlodipine and enalapril.

Among the combination therapy ACE inhibitor with diuretic was commonly used followed by β-blocker with diuretic, CCB with losartan, β-blocker with ACE inhibitor, CCB with ACE inhibitor and diuretic with hydralazine.

A DUS conducted at Majeedia hospital, New Delhi by Khurshid et al.[8] on antihypertensive drugs showed that majority of the subjects were on multiple drug therapy. Diuretics was the most frequently prescribed antihypertensive drug in overall utilization followed by β-blockers, CCBs, ACE inhibitors, ARBs and α_1-blocker. Amlodipine was the most commonly prescribed antihypertensive drug followed by atenolol, ramipril and furosemide. Among the two drug combinations most commonly used is CCBs with β-blockers followed by ACE inhibitor with Diuretics. Among the three drug combinations ACE inhibitors with β-blockers and CCBs comprised the most commonly prescribed combination.

A DUS of antihypertensive drugs done in South Malabar region of Kerala by Augustine et al.[29] showed that β-blockers are the most commonly prescribed drug group, followed by CCBs and diuretics. Atenolol, amlodipine and enalapril were the most frequently used β-blocker, CCB and ACE inhibitor respectively. Furosemide was the most commonly used diuretic. In FDC prescriptions majority were a combination of β-blocker and CCB followed by diuretic with either β-blocker or CCB or ACE inhibitor. The remaining FDCs were combinations of diuretics, ARB with ACE inhibitor or β-blocker.

A DUS by Beg et al.[30] in Uttarakhand showed that ARBs were most commonly prescribed drugs followed by ACE inhibitors, β-blockers and

CCBs. Among ARBs, the frequently used drugs were olmesartan, losartan and telmisartan. Amongst ACE inhibitors the most commonly prescribed drug was ramipril followed by enalapril. Atenolol was the most commonly prescribed β-blocker followed by metoprolol and nebivolol. Amlodipine was the only CCB prescribed. Most commonly used two drug combinations are amlodipine with atenolol followed by olmesartan with hydrochlorothiazide, losartan with hydrochlorothiazide, ramipril with hydrochlorothiazide and telmisartan with hydrochlorthiazide. Three drug combination used was olmesartan with amlodipine and hydrochlorthiazide.

A study of prescription trends and rationality of antihypertensive drugs done in Government Medical College, Jammu and Kashmir, India among Indian postmenopausal women by Tandon et al.[31] showed that as monotherapy ARBs are most commonly prescribed drugs followed by CCBs, ACE inhibitors, β-blockers and diuretics. Amlodipine among CCBs, telmisartan and losartan among ARBs, ramipril and enalapril among ACE inhibitor and atenolol and metoprolol among β-blockers were often prescribed. Among combination therapy ARB with diuretic was commonly used followed by CCBs with β-blocker.

An antihypertensive medication prescribing study by McAlister et al.[32] in 27,822 elderly Canadians with diabetes showed that ACE inhibitors, thiazide diuretics and CCBs were the commonly used antihypertensive medications.

A DUS by Liu et al.[33] showed that among newly diagnosed cases of uncomplicated hypertension in Taiwan, CCBs are most frequently prescribed antihypertensive regimens followed by β-blockers, ACE inhibitors, CCBs with

β-blockers, diuretics, CCBs with ACE inhibitors, ARBs, CCBs with ARBs and β-blockers with diuretics.

A study of antihypertensive prescribing patterns for adolescents with primary hypertension done in Michigan by Yoon et al.[34] showed that ACE inhibitor was the commonly prescribed drug as monotherapy followed by β-blocker and diuretics. The 3 most commonly prescribed drug combinations were ACE inhibitor with diuretic, combination of two diuretics and β-blocker with diuretic combinations.

A study of antihypertensive medication use among elderly patients conducted in Dhanalakshni Srinivasan Medical college and hospital, Perambalur, Tamilnadu by Gupta et al.[35] showed that CCBs were the most frequently used drugs followed by diuretics, β-blockers, ACE inhibitors and ARBs.

A DUS of antihypertensive drugs done in Coimbatore by Sakthi et al.[36] showed that among patients who were treated with monotherapy of antihypertensive drugs, CCBs was most commonly used followed by ACE inhibitors, ARBs and β-blockers. FDC used were ACE inhibitor combination with CCB and diuretics. The other major combination prescribed was β blockers with diuretics.

A DUS of antihypertensive drugs conducted in Nigeria by Kehinde et al.[37] showed that for the initiation of therapies, diuretics were the most prescribed antihypertensives either as monotherapy or in combination with other agents followed by CCBs, ACE inhibitors, centrally acting agents, β-blockers, ARBs and α-blockers. Among FDC amiloride with

hydrochlorothiazide was most frequently prescribed. In diuretics, thiazides are most frequently prescribed followed by the potassium sparing diuretics and loop diuretics.

A study of prescribing pattern of antihypertensive drugs done in Bangladesh by Sultana et al.[38] showed that ACE inhibitors are most commonly used antihypertensive drugs followed by β-blockers, ARBs, diuretics and CCBs.

A descriptive, cross-sectional survey conducted in 22 primary healthcare facilities across Trinidad by Clement et al.[39] showed that ACE inhibitors were the most commonly used class of antihypertensive drugs followed by β-blockers, diuretics and CCBs.

A prospective, cross-sectional study conducted in the Cardiology and Medicine outpatient departments by Janaki et al.[40] showed that out of 346 prescriptions, 208 prescriptions were for the newly diagnosed cases of hypertension and in that 154 prescriptions contained monotherapy and 54 prescriptions contained combined therapy. The most frequently prescribed antihypertensive drugs in these patients as monotherapy were atenolol, amlodipine, enalapril and metoprolol. Out of 54 prescriptions for the newly diagnosed cases of hypertension, 32 prescriptions contained a combination of atenolol with amlodipine and 22 prescriptions contained a combination of losartan with hydrochlorothiazide.

A DUS among hypertensive patients in a Sub-Urban hospital in Malaysia by Baig et al.[41] showed that most of the patients were on treatment with polytherapy for hypertension while rest were treated with monotherapy.

Metoprolol were the most frequently prescribed drug followed by perindopril, amlodipine, atenolol, frusemide, captopril, felodipine, chlorthiazide, nifedipine, carvedilol, losartan, ramipril, terazosin and doxazosin.

In a DUS of antihypertensive drugs in obstetric practice conducted in two tertiary care hospitals in Gulbarga city by Hooli et al.[42] showed that in a total of 200 obstetric prescriptions studied, frequency of use of nifedipine was highest followed by benzathiazide with triamterene, amlodipine, furosemide, methyldopa and spiranolactone. The use of the safest drug, methyldopa was only in 4% of patients.

In an antihypertensive drug utilisation study in hospital Tengku Ampuan Afzan, Kuantan by Azarisman et al.[43] showed that majority of patients were on either 2 or 3 antihypertensive drugs. The most frequently prescribed medications were ACE Inhibitors, CCBs, diuretics and β-blockers.

A study of prescribing pattern of antihypertensive drugs conducted in Department of Cardiology at Krishna Institute of Medical Sciences, Hyderabad by Arief et al.[44] has showed that as monotherapy, ACE inhibitors were the most commonly prescribed antihypertensive drugs followed by CCBs and diuretics. Among combination therapy often 2 drug combinations were prescribed, the most common combination was ACE inhibitor with CCB followed by β-blocker with CCB.

An observational, non-interventional, prospective study conducted at Owaisi hospital and research centre, Kanchanbagh, Hyderabad by Ghori et al.[45] showed that among the 400 hypertensive patients, 351 patients received monotherapy and only 49 patients received a combination therapy

of antihypertensive drugs. In patients receiving monotherapy, ACE inhibitors were most commonly used followed by CCBs, diuretics, β-blockers and ARB. Among all ACE inhibitors, ramipril was the most commonly prescribed. Among the CCBs the most commonly prescribed drugs were amlodipine and felodipine. Telmisartan was the most commonly prescribed ARB. A two drug combination of CCB with ACE inhibitor were prescribed to a majority of patients, followed by a combination of β-blockers with CCB, ACE inhibitor with loop diuretics and combination of two CCBs.

A study of prescription pattern of antihypertensive drugs done in the cardiology department of St. John's Medical College Hospital, Bangalore by Xavier et al.[46] showed that CCBs were most commonly prescribed, followed by ACE Inhibitors, β−blockers, diuretics, α-blockers and α_2 central agonists. Amlodipine, enalapril, metaprolol, furosemide and clonidine are the commonly used drugs in their respective groups.

A study of antihypertensive drug utilization done in Department of Cardiology, National Institute of Cardiovascular Diseases, Dhaka by Majumder et al.[47] showed that in less than 55 years old mild hypertensive patients, the most commonly used antihypertensive drugs are ACE inhibitor for males and CCB for females and in more than 55 years old mild hypertensive patients, most commonly used antihypertensive drugs are CCBs for both male and female patients. In less than 55 years old moderate hypertensive patients, the most commonly used antihypertensive drugs are ACE inhibitor for males and CCB for females and in more than 55 years old moderate hypertensive patients, the most commonly used antihypertensive drugs are CCBs for both male and female patients. In case of less than 55

years old severe hypertensive patients, the most commonly used antihypertensive drugs are combinations of ACE inhibitor with CCB and diuretic for both male and female patients and in more than 55 years old severe hypertensive patients, the most commonly used antihypertensive drugs are combinations of ACE inhibitor with CCB and diuretic for males and combinations of CCB with β-blocker for females.

A drug utilization study of antihypertensive drugs done in Germany by Pittrow et al.[48] showed that the drug classes most frequently prescribed were ACE inhibitors followed by β-blockers, diuretics, CCBs, ARBs and α-blockers.

A study of trends of physician prescriptions of the major antihypertensive classes among Chinese patients in primary care clinics in Hong Kong by Wong et al.[49] showed that among all antihypertensive drugs, CCBs and β-blockers were the most commonly prescribed drugs, followed by ACE inhibitor, α-blockers and thiazide diuretics. Among prescriptions of β blockers metoprolol and atenolol were commonly used while for CCBs, the commonest drug was nifedipine followed by diltiazem. The majority of patients were on monotherapy, followed by two class polytherapy. The most common prescription for two drug therapy consists of β-blocker with CCB polytherapy, followed by ACE inhibitor with CCB.

A DUS of antihypertensive drugs conducted in Palestine by Sweileh et al.[50] showed that out of 574 antihypertensive prescriptions 309 were males and 265 females. 277 prescriptions were based on monotherapy while 297 prescriptions were based on combination therapy. Of the monotherapy

prescriptions most commonly used was β-blockers, followed by ACE inhibitors, CCB, diuretics, ARBs, central sympatholytic and direct vasodilators. The most common two drug combination was β-blockers with diuretics followed by ACE inhibitor with diuretics, β-blockers with ACE inhibitor, ACE inhibitor with CCB, CCB with diuretics, ARBs with diuretics, β-blockers with CCB, ARB with β-blockers. Among β-blockers, the drugs used were atenolol, propranolol and metoprolol. Among ACE inhibitors, the drugs used were enalapril, captopril, benzapril and ramipril. Among CCBs, the drugs commonly used were nifedipine and amlodipine. Among diuretics, the drugs used were hydrochlorothiazide, triamterene and furosemide. Among ARBs, the drugs used were valsartan, candesartan and losartan.

A DUS of antihypertensives conducted at JJM Medical College Hospital, Davangere by Sagar et al.[51] shows that among 210 prescriptions, 126 prescriptions were of patients with hypertension alone which contain mainly CCBs followed by β blockers, ARBs, ACE inhibitors and FDCs of ARBs with hydrochlorothiazide and combination of amlodipine with hydrochlorothiazide. Eighty four prescriptions of hypertension with coexisting diabetes mellitus had mainly CCBs, ACE inhibitors, ARBs, β-blockers, and FDCs of ARBs with hydrochlorothiazide and combination of amlodipine with hydrochlorothiazide.

A retrospective, cross-sectional study of antihypertensive prescriptions of hypertensive patients admitted in Medicine inpatient wards of Kasturba Medical College Hospital, Attavar, Mangalore by Pai et al.[52] showed that majority of the patients received multiple drug therapy. CCBs were the most commonly prescribed drugs followed by diuretics, ACE inhibitors, β-blockers, ARBs, α-blockers and central sympatholytics, the leading drugs being

amlodipine, hydrochlorothiazide, enalapril, atenolol, losartan, prazosin and clonidine in the respective groups. Among those who were treated with drug combinations, 67.7% received two drugs, 27.5% received a regimen of three drugs and 4.9% received a combination of four drugs. The ARB with diuretic was the most frequently prescribed followed by a combination of two diuretics and CCBs with β-blockers. The most commonly prescribed FDCs among combination regimens were diuretics with ARBs.

A Prescription pattern study of antihypertensive drugs done in S.Nijalingappa Medical College, Bagalkot, Karnataka by Kale et al.[53] showed that CCBs were the most commonly prescribed drugs followed by diuretics, ACE inhibitors, β-blockers, ARBs, α-blockers and central sympatholytics, the leading drugs being amlodipine, hydrochlorothiazide, enalapril, atenolol, losartan, prazosin and clonidine in the respective groups.

In a DUS of antihypertensive agents conducted at the Panjab University Health Centre in India by Tiwari et al.[54] showed that more number of patients were treated with a single antihypertensive drug when compared to patients treated with antihypertensive drug combinations. Among those who were treated with two drug antihypertensive combinations a β-blocker with a CCB was commonly used followed by a β-blocker with a diuretic, a β-blocker with an ACE inhibitor, and a diuretic with a CCB. Among the monotherapy category, CCBs were commonly used followed by β-blockers, ACE inhibitors and diuretics.

A cross-sectional observational study of prescription pattern of antihypertensive drugs done in the outpatient department of Shri Sathya Sai

Medical College and Research Institute, Chennai by Maduram et al.[55] has shown that the highly prescribed single drug was amlodipine followed by enalapril, atenolol, verapamil, propranolol and metoprolol. The highly prescribed combinations of drug were amlodipine with enalapril followed by amlodipine with atenolol, amlodipine with furosemide, enalapril with furosemide, enalapril with atenolol, enalapril with verapamil, amlodipine with propranolol and amlodipine with metoprolol. The drugs prescribed in three drugs combinations were amlodipine, enalapril and atenolol or nifedipine or furosemide or metoprolol and the other combination of atenolol and furosemide, enalapril or metoprolol. The patients with asthma and DM were commonly prescribed either enalapril or amlodipine.

A prescription pattern study of antihypertensive drugs conducted in General medicine department at Sri Muthukumaran Medical college Hospital and Research Institute, Chikarayapuram, Chennai by Janagan et al.[56] has shown that patients receiving combination antihypertensive agents were more than those receiving monotherapy. In patients receiving monotherapy, ACE inhibitors were commonly prescribed class followed by ARBs, cardioselective β-blockers, CCBs and diuretics. In combination therapy, ACE inhibitors with thiazide diuretics are the most commonly prescribed combination followed by ARBs with thiazide diuretics, ACE inhibitors with CCBs and ARBs with β blockers. The three drug regimen used was ACE inhibitor with thiazide diuretic and β blockers.

A DUS of antihypertensive drugs conducted in Chandigarh by Dhanaraj et al.[57] showed that majority of the patients were on combination therapy followed by monotherapy. Among the patients on combination therapy two

drug combination was commonly preferred followed by three and four drug combination therapy. Patients on monotherapy were mostly receiving ACE inhibitors and ARBs followed by β-blockers. In two drugs combination therapy, ACE inhibitors with ARBs or diuretics were commonly used followed by ARBs with diuretics, ACE inhibitors with CCBs, and ARB with CCBs. In three drug combinations, combination of ACE inhibitors with ARB and diuretics were highest followed by ARB with CCB and diuretics. In 4 or more drug combinations of ARB, ACE inhibitor, CCBs with diuretics were commonly prescribed.

A DUS of antihypertensive drugs conducted in Jordan by Al-Drabah et al.[58] showed that majority of the patients were on monotherapy of antihypertensive drugs followed by two drug, three drug and four drug combination therapy. Among patients receiving monotherapy ACE inhibitors was most commonly used followed by β-blockers, CCBs, ARBs and diuretics. Among patients on two drug combination therapy most commonly used combination was a diuretic with a β-blocker followed by an ACE inhibitor with a β-blocker. In patients on three drug combination therapy diuretic with a β-blocker and ARB was commonly used. Patients on four drug combination therapy the most frequently used combinations included a diuretic, an ACE inhibitor, a β-blocker and a CCB.

A drug utilization study of hypertensive patients conducted in Punjab by Bajaj et al.[59] showed that diuretics was the most commonly prescribed group of antihypertensive drugs followed by ARBs, β-blockers and CCBs. Out of diuretics, thiazides group was the most commonly used. Majority of the patients were on combination therapy.

A DUS of antihypertensive drugs conducted at Warangal, India by Pavani et al.[60] revealed that majority of the patients were on two drug combination therapy followed monotherapy and triple therapy. In multiple drug therapy, maximum number of patients were prescribed with FDCs. Among patients who underwent monotherapy majority of the patients were prescribed with ARBs followed by CCBs, ACE inhibitors, diuretics and β-blockers. Among patients in whom two antihypertensives were prescribed, majority of the patients were prescribed with a combination of diuretics and ARBs followed by diuretics and ACE inhibitors and diuretics and β-blockers. Results of the triple therapy revealed that, maximum number of the patients were prescribed with diuretics along with ARBs and β-blockers, followed by diuretics with ARBs and ACE inhibitors and diuretics with ARBs and CCBs.

A DUS of antihypertensive drugs done in Vadodara, India by Shah et al.[61] showed that majority of hypertensive patients were on monotherapy followed by two and three drug combination therapy. Patients on monotherapy mostly received ACE inhibitor or ARB followed by β-blockers, CCBs, thiazide diuretics and combined α and β blockers. Most common prescribed combinations were amlodipine with atenolol, losartan with hydrochlorthiazide and metoprolol with amlodipine. Most commonly used multi drug combination therapy was CCB with β-blocker followed by ARB with diuretic, CCB with diuretic, ARB with CCB and ARB with diuretic and combined α and β blocker.

A DUS of antihypertensive drugs conducted in Andhra Pradesh by Sindhu et al.[62] majority of hypertensive patients were on two drug combination therapy followed by monotherapy and patients on three drug

combination therapy. In that most of the drug prescriptions were as FDCs. CCBs were the commonly prescribed drugs as monotherapy followed by ARBs, ACE inhibitors, β-blockers and diuretics. Among patients on two drug combination therapy ARBs with diuretics were the mostly prescribed combination followed by β-blocker with CCBs. Diuretics with ARBs and CCBs was the commonly prescribed three drug combination.

A drug utilization study of antihypertensive drugs conducted at Deccan College of Medical Sciences, Hyderabad by Sandozi et al.[63] was conducted as 2 phases between 2008 and 2009-10. Out of 300 cases recorded in Phase 1, 47% were men and 53% were women. Majority of the patients were on monotherapy of antihypertensive drugs. The most commonly prescribed drug was CCB, amlodipine followed by β-blockers atenolol and metaprolol, ACE inhibitors, diuretics and ARBs. 84 out of 300 patients had associated DM. In that most of the patients were on monotherapy of ACE inhibitors followed by β-blockers, CCBs and ARBs. Commonly used combination was ACE inhibitors with diuretics. Out of 450 patients recorded in phase 2, majority of the patients were men. 105 of these were having DM. Most of the patients were on monotherapy and most prescribed drugs were ACE inhibitors followed by CCBs, β-blockers, ARBs and diuretics. Commonly used combinations were β-blockers with CCBs, ACE inhibitors with diuretics and ARBs with diuretics.

A prescription pattern study of antihypertensive drugs conducted at Indirapuram, Ghaziabad (U.P) by Bhardwaj et al.[64] showed that ARBs and diuretics were the most commonly prescribed drugs followed by β-blockers, CCBs and ACE inhibitors. Among the 37 patients prescription, majority was

prescribed as monotherapy and some as combination therapy. Most commonly prescribed drug in monotherapy were amlodipine, telmisartan and indapamide and nebivolol, losartan and olmesartan were least prescribed. Most commonly prescribed drug in combination therapy was hydrochlorthiazide and telmisartan.

A DUS of antihypertensive drugs conducted in South India by John et al.[65] showed that among the antihypertensive drugs prescribed CCBs, β-blockers and ACE inhibitors represented the major classes. CCBs (amlodipine) were the most widely used antihypertensive followed by β-blockers. Amlodipine was the single most commonly prescribed antihypertensive drug followed by metoprolol.

A DUS of antihypertensive drugs conducted by Fretheim et al.[66] showed that CCBs and ACE inhibitors were the most commonly used drugs for the treatment of hypertension.

4.7. Studies related to Pharmacovigilance of antihypertensive drugs:

A study of ADRs due to antihypertensive drugs conducted in Majeedia Hospital at Hamdard University Campus in New Delhi by Hussain et al.[67] ADRs were more common in females than males. The most vulnerable age group was 41–50 years with respect to ADRs followed by 51-60 years, 61-70 years, 31-40 years, >70 years and 20-30 years. More ADRs were reported in patients receiving combination therapy when compared to patients on monotherapy. Among the systems affected, ADRs commonly affected cardiovascular system followed by gastrointestinal system and respiratory system. On WHO scale of causality assessment most of the ADRs were

possible followed by probable and unlikely. Commonly experienced ADRs in the patients on β-blockers was hypotension, headache, giddiness and bradycardia in patients on atenolol and bronchospasm, impotence, and irritation over whole body seen in patients on metoprolol and pedal edema with nebivolol. Dry cough was the only ADR observed with ACE inhibitors mainly due to enalapril and ramipril. ADRs experienced with the use of CCBs were pedal oedema, swelling of the face, generalised oedema, headache, and giddiness with the use of amlodipine and bradycardia with the use of nifidipine. In this study it was found that β-blockers were most frequently associated with ADRs followed by ACE inhibitors and CCBs.

A study of ADRs due to antihypertensive drugs conducted in New Delhi by Khurshid et al.[10] showed that out of 192 patients, 13 developed ADRs. Prevalence of ADRs due to antihypertensive drugs was found to be more infemales. The most vulnerable age group was 41–50 years with respect to ADRs followed by 71–80 years, 51–60 years, 31–40 years and 61–70 years. CCBs were commonly associated with ADRs followed by diuretics, β-blockers, ARBs and ACE inhibitors. Among individual drugs amlodipine was frequently ADRs followed by torasemide and ramipril. The common ADRs seen with the use of amlodipine were abdominal pain, pedal oedema, drowsiness and back pain. Common complaints with torasemide were fatigue, visual impairment and dizziness. Dry cough was the most frequent ADR observed with ramipril. Naranjo's probability scale showed that most of the ADRs were possible followed by probable and a few as unlikely. ADRs associated with central nervous system were most common followed by musculo-skeletal complaints and gastrointestinal disorders.

A study of ADRs associated with the use of antihypertensive drugs conducted in Gujarat, India by Joshi et al.[68] showed that all hypertensive drugs caused dizziness, ankle swelling, headache, fatigue, chest discomfort and cough. Erectile dysfunction was the adverse effect of thiazide diuretics. Severe hypotension occurred after initial doses of any ACE inhibitor. Infrequent ADRs were associated with ARBs which included first dose orthostatic hypotension, diarrhea, rash and dyspepsia. ADRs associated with the use of β-blockers included nausea, bronchospasm, diarrhea, dyspnea and cold extremities. The most common side effects caused by the CCBs included dizziness, headache, hypotension, flushing, digital dysesthesia and nausea.

A study of ADRs due to antihypertensive drugs done in outpatient department of rural medical hospital in Loni, India by Kale et al.[69] showed that common adverse drug reactions were dry cough, weakness, headache, mild dizziness, dryness of mouth and ankle swelling.

A study of ADRs due to antihypertensive drugs done in BRD Medical College, Gorakhpur, India by Upadhayai et al.[70] showed that out of 1147 patients who were on antihypertensive drugs 54 patients developed skin reactions. Maximum number of patients with adverse cutaneous drug reactions (ACDR) was seen with atenolol followed by amlodipine. The most common type of ACDR was urticaria followed by lichenoid drug eruption.

A study of ADRs in hypertensive patients in a primary care setting done in Mexican Institute of Social Security, Mexico by Mino-Leon et al.[71] has shown that ADRs seen with the use of captopril are somnolence, cough,

dizziness, headache, anxiety and fatigue. ADRs with enalapril are cough and paresthesia. ADRs seen with the use of metoprolol are confusion, nervousness and somnolence. Headache and fatigue were seen in patients on verapamil. Nifedipine caused dizziness, headache and paresthesia.

A study of ADRs due to antihypertensive drugs conducted at Jordan by Al-Drabah et al.[58] showed that the most frequent ADRs related to the use of antihypertensive drugs were postural hypotension followed by lower limb edema and palpitations.

A retrospective evaluation of ADRs at Pugliese-Ciaccio Hospital of Catanzaro, Italy by Rende et al.[72] has shown that common ADRs recorded in patients taking antihypertensive drugs are hypotension, hyponatremia, cough, hyperkalemia, hypokalemia and swollen foots.

A study of ADRs due to antihypertensive drugs conducted in Warangal, Andhra Pradesh by Sindhu et al.[62] showed that among 205 patients recruited 85 patients reported to have adverse effects. Commonest ADR was dizziness, followed by nausea, edema and dry cough.

A study of ADRs due to antihypertensive drugs carried out in medical ICU of hospital in South India by John et al.[65] showed that the commonly encountered ADRs to the antihypertensive drugs were dyselectrolytemia by enalapril and drug induced bradycardia by metoprolol.

An ADR monitoring study of telmisartan in hypertensive patients conducted in Maharashtra by Suhas et al.[73] has shown that headache, respiratory infection, giddiness, pain, weakness, gastrointestinal tract

problems, sinusitis, pharyngitis, indigestion, muscle pain, cough and urinary tract infection as the common ADRs.

An ADR monitoring study of antihypertensive drugs conducted in UAE by Alomar et al.[74] has reported that ADRs during the study were headache, giddiness and ankle oedema, breathlessness, gastrointestinal tract problems and muscle pain.

A study of evaluation of the relative incidence of ADRs leading to treatment discontinuation of recommended antihypertensive drugs carried out at the cardiology unit of the Department of Medicine, University of Maiduguri teaching hospital, Nigeria by Ibn et al.[75] has shown that cough was the reason cited for discontinuation of ACE inhibitors, peripheral oedema was seen with CCBs and bradycardia was seen with β-blockers. Diuretics showed the lowest discontinuation rate mainly due to hypokalemia.

A study of ADRs to antihypertensive drugs done in Raja Muthiah medical college, Annamalai University, Chidambaram, Tamilnadu by Basak et al.[76] reported that CCB as most common antihypertensive drug group responsible for ADR followed by ACE inhibitors and β-blockers. The ADRs to CCBs observed were dizziness, fatigue, dyspepsia and headache. ADRs to ARBs were dizziness and tachycardia. Huperuricemia, hypokalemia and muscle cramp was seen with the use of diuretics. ADRs seen with the use of ACE inhibitors were dry cough, headache and vomiting.

5. Materials and methods:

5.1. Study design:

This study was a cross sectional study.

5.2. Study setting:

This study was conducted at Department of General Medicine, Sree Mookambika Institute of Medical Sciences, Kulasekharam, Kanyakumari district, Tamilnadu.

5.3. Time of the study:

This study was done over a period of 6 months during the time period of October 2013 and March 2014.

5.4. Inclusion criteria:

i. Patients receiving antihypertensive drugs from Medicine Department from October 2013 to March 2014
ii. Patients of all age groups and both sexes

5.5. Exclusion criteria:

i. Patients already recruited in the study coming for refill of antihypertensive drugs

5.6. Institutional Human Ethics Committee (IHEC) Approval:

The study proposal was approved by the Institutional Human Ethics Committee (IHEC) of SMIMS with Ref. No. SMIMS/IHEC/2013/A/22. The certificate of approval for the same has been enclosed in the annexure.

5.7. Procedure:

The study was carried out in Medicine department of SMIMS, after getting approval from the Institutional Research Committee (IRC) and Institutional Human Ethics Committee (IHEC). Patients visiting the Medicine

department of the institution was included in this study after satisfying the inclusion and exclusion criteria, they were explained in detail about the study and informed written consent was obtained from each patient before recruiting them into the study. Details of prescribed antihypertensive drugs like formulation, whether drug is prescribed using brand name or generic name, dose, route of administration, drugs taken before or after food, frequency, duration of the treatment, any adverse drug reactions, cost of drugs prescribed, any other co-morbid conditions and any other associated medications taken concurrently were recorded in the case record form.

5.8. Data analysis and Presentation:

A. Data obtained from case record form is presented as
   i. Number of patients receiving antihypertensive drug as monotherapy
   ii. Number of patients receiving antihypertensive drugs as combination therapy
   iii. Number of patients receiving different classes of antihypertensive drugs like thiazide diuretics, ACE inhibitors, CCBs, α and β blockers, ARBs, vasodilators etc.
   iv. Number of prescriptions of antihypertensive drugs by generic and brand names.
B. Cost of antihypertensive drugs which will be more economically viable and which will be more expensive for the patient.
C. Number of patients who experienced different ADRs for different classes of antihypertensive drugs.

D. Casuality assessment of ADRs reported in patients prescribed with antihypertensive drugs by using WHO-UMC causality assessment scale and Naranjo scale.

i. WHO-UMC system for causality assessment[26]:

Certain:

- Event or laboratory test abnormality, with plausible time relationship to drug intake
- Cannot be explained by disease or other drugs
- Response to withdrawal plausible
- Event definitive pharmacologically or phenomenologically
- Rechallenge satisfactory, if necessary

Probable/ Likely:

- Event or laboratory test abnormality, with reasonable time relationship to drug intake
- Unlikely to be attributed to disease or other drugs
- Response to withdrawal clinically reasonable
- Rechallenge not required

Possible:

- Event or laboratory test abnormality, with reasonable time relationship to drug intake
- Could also be explained by disease or other drugs
- Information on drug withdrawal may be lacking or unclear

Unlikely:

- Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable
- Disease or other drugs provide plausible explanations

Conditional/ Unclassified:

- Event or laboratory test abnormality
- More data for proper assessment needed, or
- Additional data under examination

Unassessable/ Unclassifiable:

- Report suggesting an adverse reaction
- Cannot be judged because information is insufficient or contradictory
- Data cannot be supplemented or verified

ii. Naranjo Causality Scale[26]:

a. Are there previous conclusive reports on this reaction?

   Yes (+1), No (0), Do not know or not done (0)

b. Did the adverse event appear after the suspected drug was given?

   Yes (+2), No (-1), Do not know or not done (0)

c. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?

   Yes (+1), No (0), Do not know or not done (0)

d. Did the adverse reaction appear when the drug was readministered?

   Yes (+2), No (-1), Do not know or not done (0)

e. Are there alternative causes that could have caused the reaction?

   Yes (-1), No (+2), Do not know or not done (0)

f. Did the reaction reappear when a placebo was given?

Yes (-1), No (+1), Do not know or not done (0)

g. Was the drug detected in any body fluid in toxic concentrations?

Yes (+1), No (0), Do not know or not done (0)

h. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?

Yes (+1), No (0), Do not know or not done (0)

i. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?

Yes (+1), No (0), Do not know or not done (0)

Scoring

> 9 = definite ADR

5-8 = probable ADR

1-4 = possible ADR

0 = doubtful ADR

E. Severity assessment of ADRs due to antihypertensive drugs by **Hartwig severity scale**.[28]

Mild:

Level 1: The ADR requires no change in treatment with the suspected drug. OR

Level 2: The ADR requires that the suspected drug be withheld, discontinued or otherwise changed. No antidote or other treatment is required and there is no increase in length of stay.

Moderate:

Level 3: The ADR requires that the suspected drug be withheld, discontinued or otherwise changed, and/ or an antidote or other treatment is required. There is no increase in length of stay. OR

Level 4 (a): Any level 3 ADR that increases length of stay by at least one day. OR

Level 4 (b): The ADR is the reason for admission.

Severe:

Level 5: Any level 4 ADR that requires intensive medical care. OR

Level 6: The ADR causes permanent harm to the patient. OR

Level 7: The ADR either directly or indirectly leads to the death of the patient.

F. Preventability criteria of ADRs due to antihypertensive drugs by **Schumock and Thornton scale**.[27]

Definitely Preventable:

1. Was there a history of allergy or previous reactions to the drug?
2. Was the drug involved inappropriate for the patient's clinical condition?
3. Was the dose, route or frequency of administration inappropriate for the patient's age, weight or disease state?
4. Was a toxic serum drug concentration (or laboratory monitoring test) documented?

5. Was there a known treatment for the ADR?

Probably Preventable:

6. Was required Therapeutic drug monitoring or other necessary laboratory tests not performed?
7. Was a drug interaction involved in the ADR?
8. Was poor compliance involved in the ADR?
9. Were preventative measures not prescribed or administered to the patient?

Not preventable:

If all above criteria not fulfilled

6. Results:

The present cross-sectional study of drug utilization pattern and adverse drug reaction profile of antihypertensive drugs was done at the Department of Medicine, Sree Mookambika Institute of Medical Sciences, Kulasekharam, Tamilnadu, for a period of 6 months (from October 2013 to March 2014). Total of 127 prescriptions and 86 ADRs were collected and analysed. In this study it was noted that in all prescriptions lifestyle modifications were recommended for all patients with hypertension irrespective of antihypertensive drug therapy. In all the prescriptions recorded, the route of administration of antihypertensive drugs was oral.

6.1. Age distribution of patients studied:

In the current study out of 127 patients, 65 patients (51.18%) belonged to age group of 61-70 years. There were 34 patients (26.77%) in age group of 51-60 years, 16 patients (12.6%) in age group of 71-80 years, 10 patients (7.87%) in age group of 41-50 years and 2 patients (1.58%) in age group of 81-90 years as shown in Table 1.

6.2. Gender distribution of patients studied:

In the current study out of 127 patients, 32 (25.2%) were male and 95 (74.8%) were female as shown in Table 1.

6.3. Body mass index of patients studied:

Calculation of body mass index showed that out of 127 patients, 73 (57.48%) were of normal weight, 44 (34.65%) were overweight and 10 (7.87%) were underweight as shown in Table 1.

6.4. Socioeconomic status of patients studied:

Socioeconomic status of the patients studied were grouped as per their monthly per capita income according to modified Prasad classification 2013.[77] Out of 127 patients, 67 (52.76%) belonged to class III. Number of patients in other classes were 34 (26.77%) in class IV, 11 (8.66%) in class II, 8 (6.3%) in class V and 7 (5.51%) in class I as shown in Table 2.

6.5. Co-morbid conditions:

In the current study, out of 127 patients, 84 had co-morbid conditions. Out these 84 patients, 33 (39.28%) were suffering from concurrent diabetes mellitus. Other associated co-morbid conditions were COPD in 22 patients (26.19%), DM with COPD in 11 patients (13.1%), CAD in 11 patients (13.1%), Dyslipidaemia in 3 patients (3.57%), CVA in 2 patients (2.38%), Mitral stenosis in 1 patient (1.19%) and Hypothyroidism in 1 patient (1.19%) as shown in Table 2.

6.6. Drugs prescribed by generic and brand name:

In the present study, in all the 127 prescriptions, all the antihypertensive drugs were prescribed by brand name as shown in Figure 1.

6.7. Number of patients receiving monotherapy or combination drug therapy of antihypertensive drugs:

In the current study, there were total 127 prescriptions of antihypertensive drugs. Among 127 prescriptions, 96 (75.59%) were monotherapy and 31 (24.41%) were combination therapy. Among the prescriptions of antihypertensive drugs as combination therapy 22 (17.32%), 7 (5.51%) and 2

(1.58%) were combination of two, three and four drugs respectively. The details of patients receiving monotherapy or combination drug therapy has been depicted in Figure 2.

6.8. Number of patients receiving monotherapy of antihypertensive drugs:

In present study 96 (75.59%) patients had received single drug for the treatment of hypertension. Amlodipine was the most commonly used drug which was prescribed for 84 (87.5%) patients. Other drugs prescribed as monotherapy were ramipril for 3 (3.14%) patients, nifedipine for 2 (2.08%) patients, telmisartan for 2 (2.08%) patients, metoprolol for 2 (2.08%) patients, losartan for 1 (1.04%) patient, nebivolol for 1 (1.04%) patient and furosemide for 1 (1.04%) patient as shown in Figure 3.

6.9. Number of patients receiving two drug combination therapy of antihypertensive drugs:

Out of 127 patients two drugs were prescribed for 22 (17.32%) patients. Amlodipine + atenolol was most commonly prescribed two drug combination which was prescribed for 6 patients (27.26%). Other two drug combinations prescribed were amlodipine + furosemide for 5 patients (22.72%), telmisartan + hydrochlorothiazide for 3 patients (13.63%), amlodipine + ramipril for 2 patients (9.09%), enalapril + hydrochlorothiazide for 1 patient (4.55%), amlodipine + losartan for 1 patient (4.55%), telmisartan + amlodipine for 1 patient (4.55%), losartan + hydrochlorothiazide for 1 patient (4.55%), carvedilol + ramipril for 1 patient (4.55%) and amlodipine + nebivolol for 1 patient (4.55%) as shown in Figure 4.

6.10. Number of patients receiving three drug therapy of antihypertensive drugs:

Out of 127 prescriptions three drugs were prescribed for 7 (5.51%) patients. In that losartan + hydrochlorothiazide + amlodipine was the most commonly prescribed three drug combination prescribed for 3 patients (42.84%). Other three drug combinations prescribed were ramipril + amlodipine + atenolol for 1 patient (14.29%), amlodipine + atenolol + furosemide for 1 patient (14.29%), bisoprolol + ramipril + furosemide for 1 patient (14.29%) and telmisartan + amlodipine + hydrochlorothiazide for 1 patient (14.29%) as shown in Figure 5.

6.11. Number of patients receiving four drug therapy of antihypertensive drugs:

The four drug combinations were the least prescribed. Four drugs were prescribed only for 2 (1.58%) patients. Telmisartan + hydrochlorothiazide + amlodipine + atenolol and telmisartan + hydrochlorothiazide + amlodipine + metoprolol were the two four drug combinations prescribed for 2 patients as shown in Figure 6.

6.12. Expenditure of medications prescribed:

In present study at each visit antihypertensive drugs were prescribed for a period of one month. Metoprolol was the most expensive and furosemide was the least expensive drug prescribed as monotherapy. Telmisartan + hydrochlorothiazide + amlodipine was the most expensive and amlodipine + furosemide was the least expensive drug prescribed as combination therapy. Of all the brands of antihypertensive drugs prescribed, the cheapest was Lasix

(furosemide) for which the expenditure per month was INR 6.36 and the most expensive was the three drug combination of Telma H + Avacard (telmisartan + hydrochlorothiazide + amlodipine) for which the expenditure per month was INR 524.82 as shown in figure 7, 8 and 9.

6.13. Adverse drug reactions recorded:

In present study it has been observed that 86 ADRs developed for different types of antihypertensive drugs during the period of six months from October 2013 to March 2014.

6.14. Gender distribution of patients developing ADRs to antihypertensive drugs:

Among 86 patients who showed ADRs to antihypertensive drugs, 55 (63.95%) were female and 31 (36.05%) were male as shown in Figure 10.

6.15. Age distribution of patients developing ADRs to antihypertensive drugs:

ADRs to antihypertensive drugs were observed most commonly in age group of 61–70 years (n = 40, 46.51%). Other age groups affected were 51–60 years (n = 24, 27.91%), 71–80 years (n = 13, 15.12%) and 41–50 years (n = 9, 10.46%) as shown in Figure 11.

6.16. Number of patients on monotherapy and combination therapy developing ADRs shown with antihypertensive drugs:

Out of 86 patients who developed ADRs while receiving antihypertensive therapy, 36 (41.86%) were receiving monotherapy and 50 (58.14%) were receiving combination therapy as shown in Figure 12.

6.17. ADRs shown on treatment with different classes of antihypertensive drugs:

CCBs were found to be the commonest therapeutic class of antihypertensive drugs associated with ADRs (n = 54, 62.79%). Other groups associated with ADRs were ARBs (n = 11, 12.79%), β-blockers (n = 10, 11.63%), ACE inhibitors (n = 6, 6.98%) and diuretics (n = 5, 5.81%) as shown in Figure 13. Among individual drugs amlodipine was found to be the commonest drug associated with ADRs (n = 41).

6.18. ADRs to antihypertensive drugs affecting various systems:

In present study ADRs to antihypertensive drugs associated with central nervous system (n = 37, 43.03%) were found to be the most frequent [headache, dizziness, sedation and giddiness]. Other systems associated with ADRs were musculo-skeletal system (n = 25, 29.07%) [pedal edema, fatigue and muscle cramp], respiratory system (n = 11, 12.79%) [dry cough and breathlessness], gastrointestinal system (n = 8, 9.3%) [abdominal pain and diarrhoea], cardiovascular system (n = 4, 4.65%) [bradycardia] and skin (n = 1, 1.16%) [irritation all over the body] as shown in Figure 14.

6.19. WHO causality assessment scale:

According to WHO causality assessment scale most of the ADRs were “probable” 44 (51.16%), followed by “possible” 28 (32.56%), unclassifiable 10 (11.63%) and unlikely 4 (4.65%) as shown in Figure 15.

6.20. Naranjo scale:

According to Naranjo scale 67 (77.91%) ADRs were “Possible”, 19 (22.09%) were “Probable” and none were “Definite” as shown in Figure 16.

6.21. Hartwig and Siegel severity assessment scale:

According to Hartwig and Siegel severity assessment scale 87.21% ADRs (n = 75) were “mild”, 12.79% ADRs (n = 11) were “moderate” and none of the ADRs were “severe” as shown in Figure 17.

6.22. Modified Schumock and Thornton preventability scale:

According to Modified Schumock and Thornton preventability scale 33.72% (n = 29) ADRs were “Definitely preventable” while 66.28% (n = 57) ADRs were “Probably preventable” and none of the ADRs were “Not preventable” as shown in Figure 18.

Table 1: Demographic profile of the patients studied

Sl. No.			
1.	**Age in years**		**Number of patients**
	i.	41 - 50	10
	ii.	51 - 60	34
	iii.	61 - 70	65
	iv.	71 - 80	16
	v.	81 - 90	2
2.	**Sex**		
	i.	Male	95
	ii.	Female	32
3.	**Body mass index** in Kg/m^2		
	i.	Normal weight (18.5 – 24.9)	73
	ii.	Overweight (25 – 29.9)	44
	iii.	Underweight (<18.5)	10

Table 2: Socioeconomic status and comorbid conditions of the patients studied

Sl. No.			
1.	**Socioeconomic status** (Prasad classification)		**Number of patients**
	i.	Class I	7
	ii.	Class II	11
	iii.	Class III	67
	iv.	Class IV	34
	v.	Class V	8
2.	**Comorbid conditions**		
	i.	DM	33
	ii.	COPD	22
	iii.	DM + COPD	11
	iv.	CAD	11
	v.	Dyslipidaemia	3
	vi.	CVA	2
	vii.	Hypothyroidism	1
	viii.	Mitral stenosis	1

DM :Diabetes Mellitus

COPD :Chronic Obstructive Pulmonary Disease

CAD :Coronary Artery Disease

CVA :Cerebral Vascular Accident

Prasad classification 2013[77]

Class I :Rs 5156 and above*

Class II :Rs 2578 – 5155*

Class III :Rs 1547 – 2577*

Class IV :Rs 773 – 1546*

Class V :Below Rs 773*

*Per capita monthly income

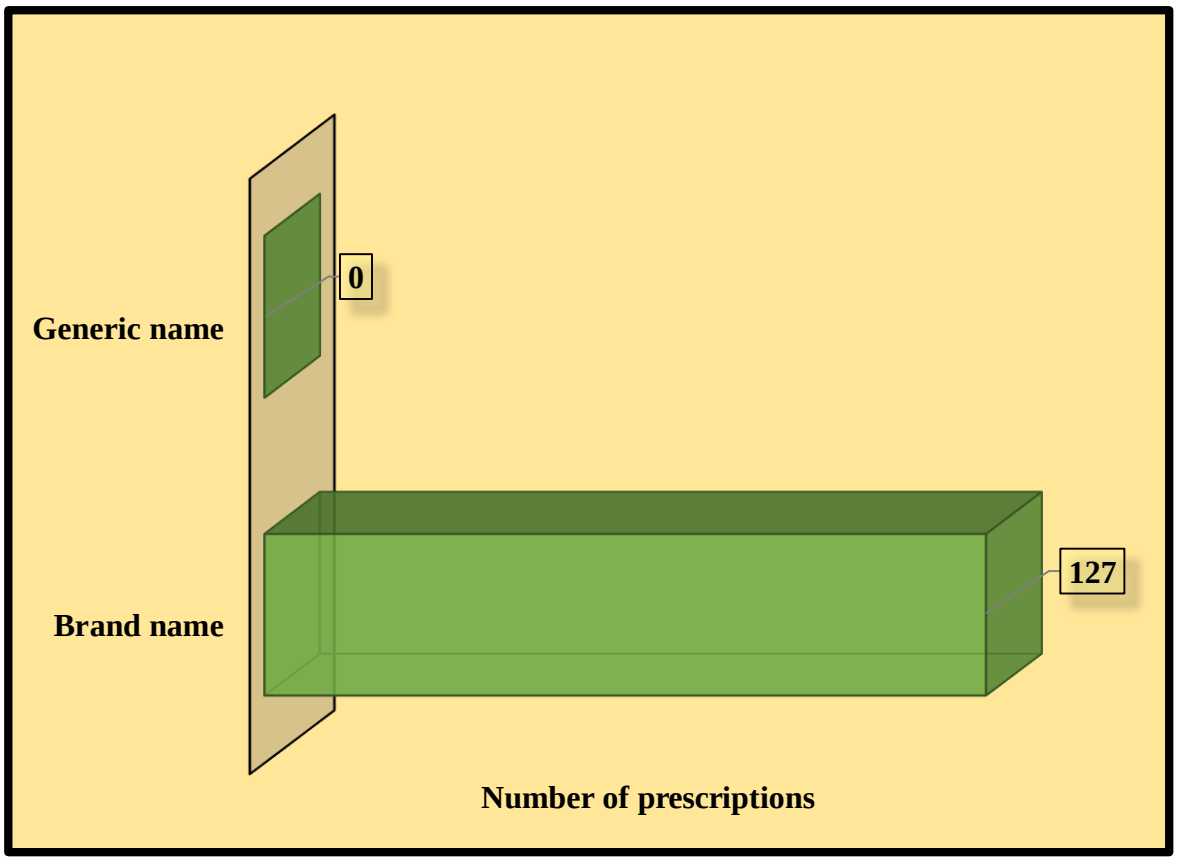

Figure 1. Bar diagram showing the number of prescriptions of antihypertensive drugs by generic and brand names

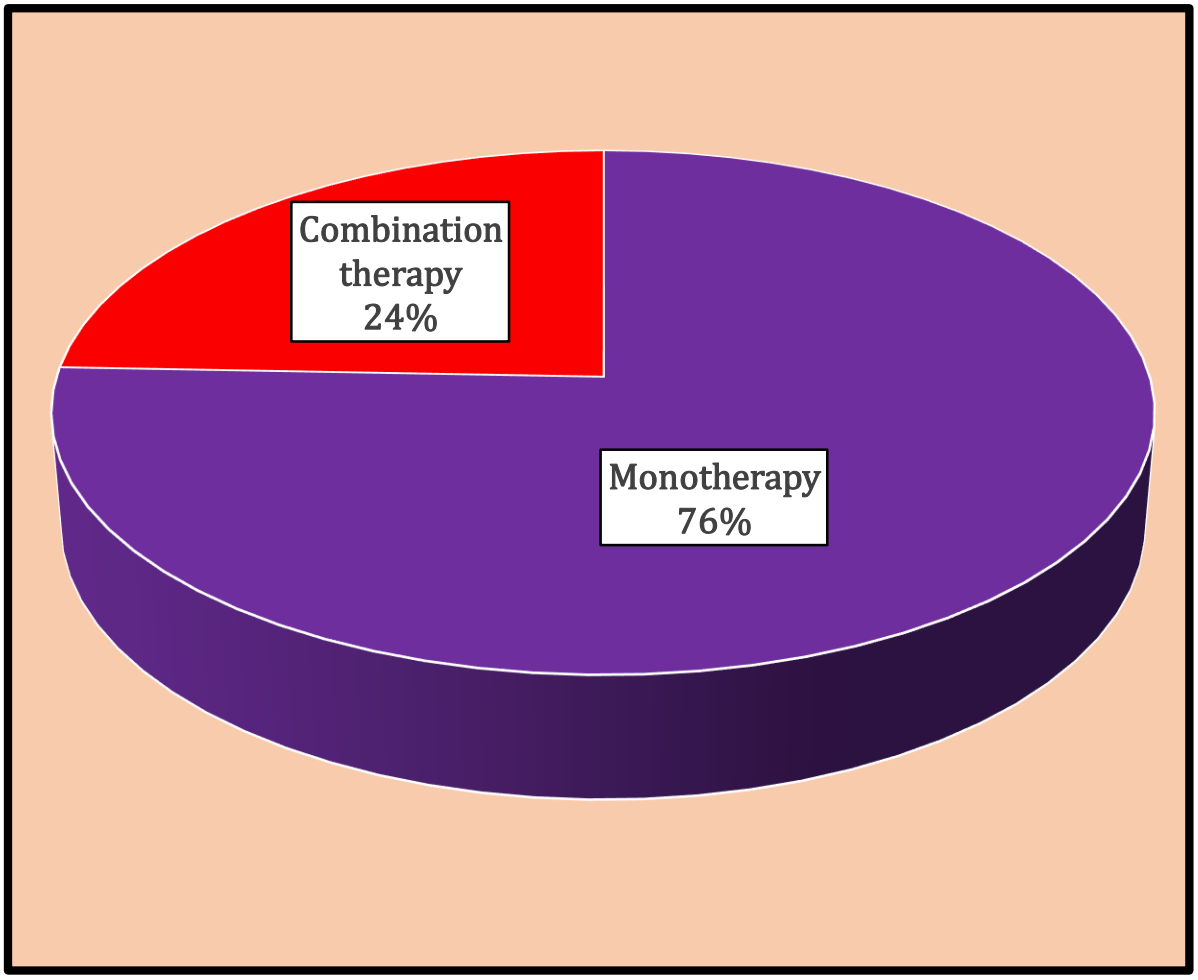

Figure 2. Pie diagram showing the percentage of prescriptions of antihypertensive drugs as monotherapy and combination therapy

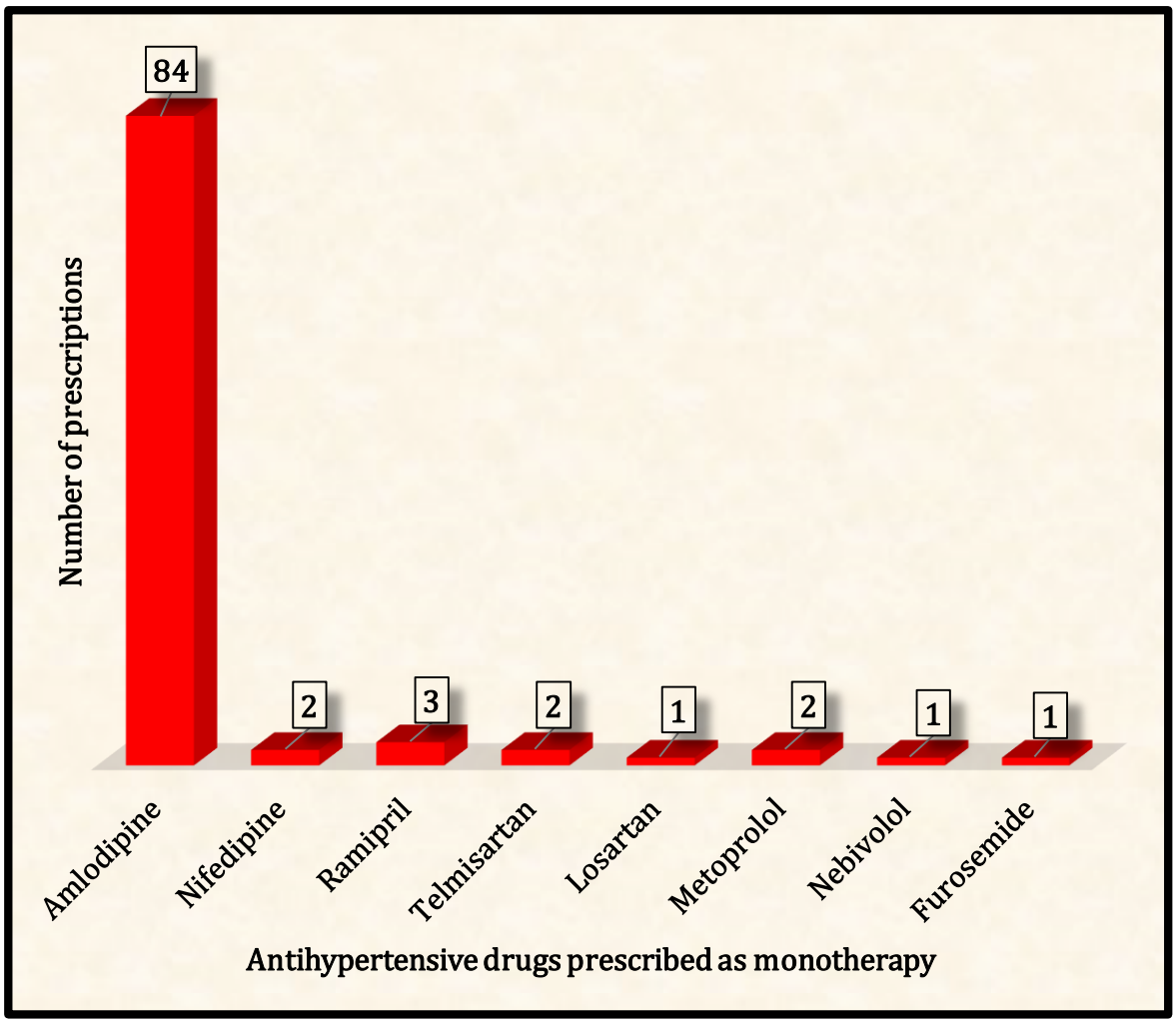

Figure 3. Bar diagram showing the number of prescriptions of antihypertensive drugs as monotherapy

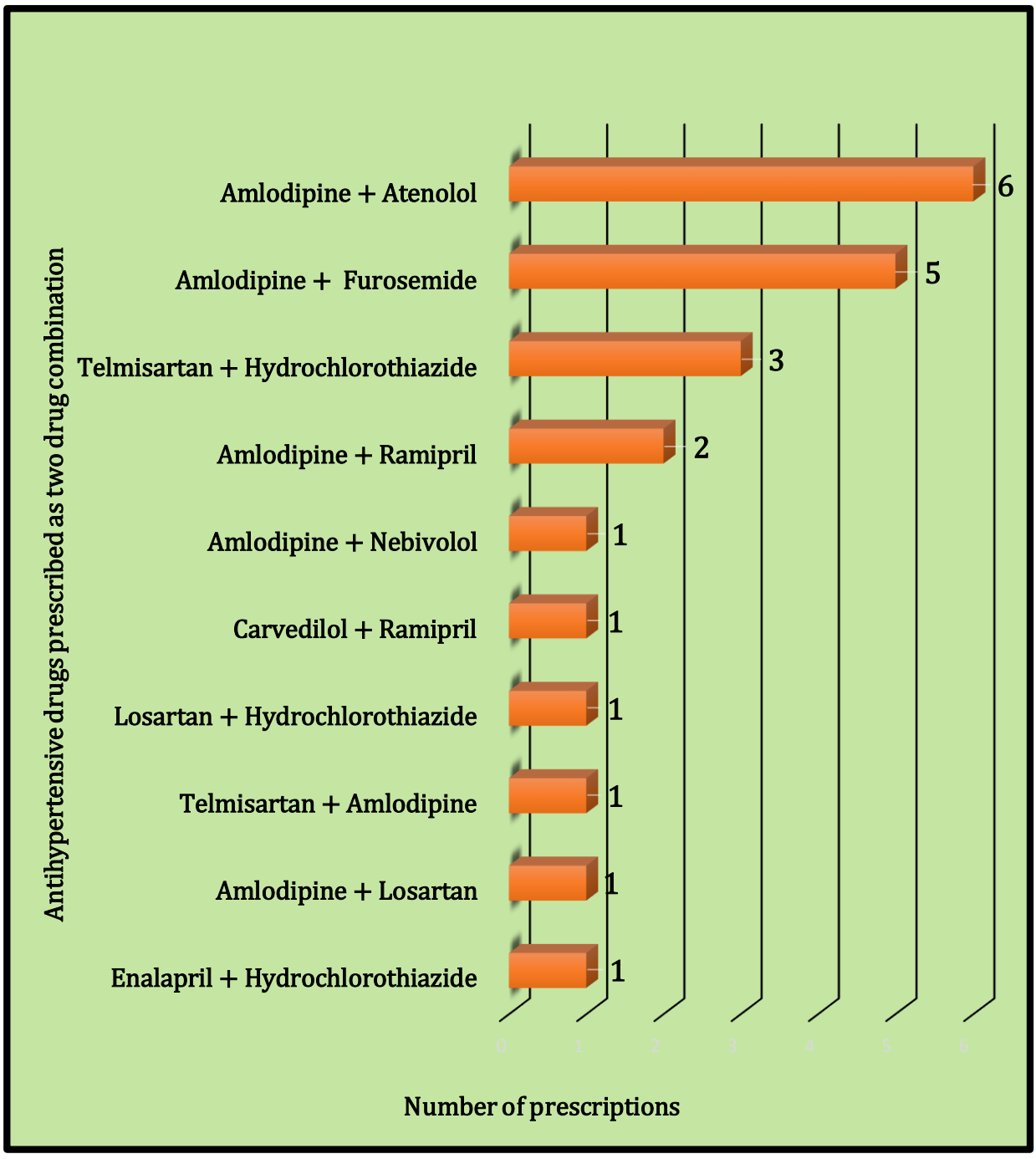

Figure 4. Bar diagram showing the number of prescriptions of antihypertensive drugs as two drug combination therapy

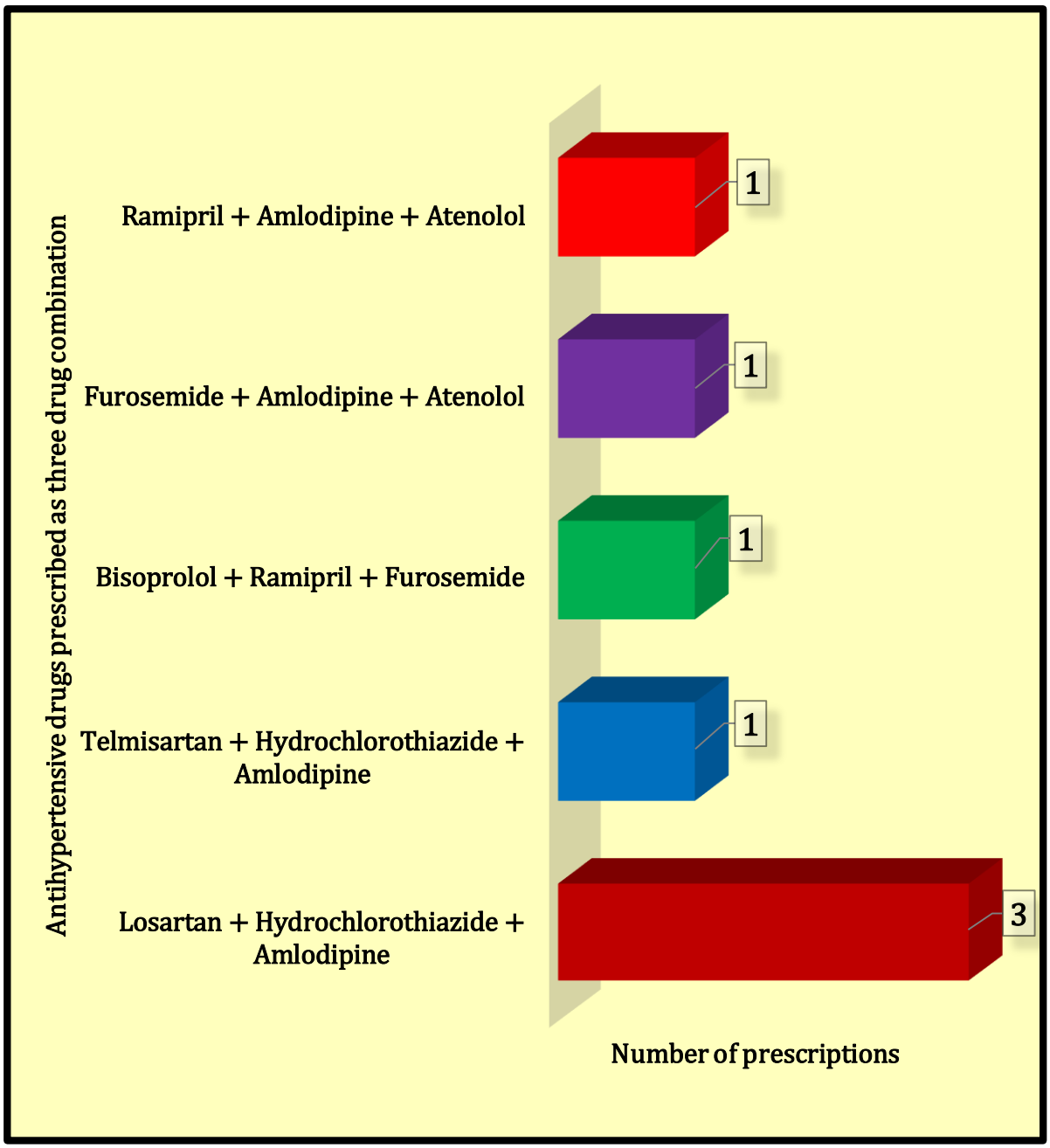

Figure 5. Bar diagram showing the number of prescriptions of antihypertensive drugs as three drug combination therapy

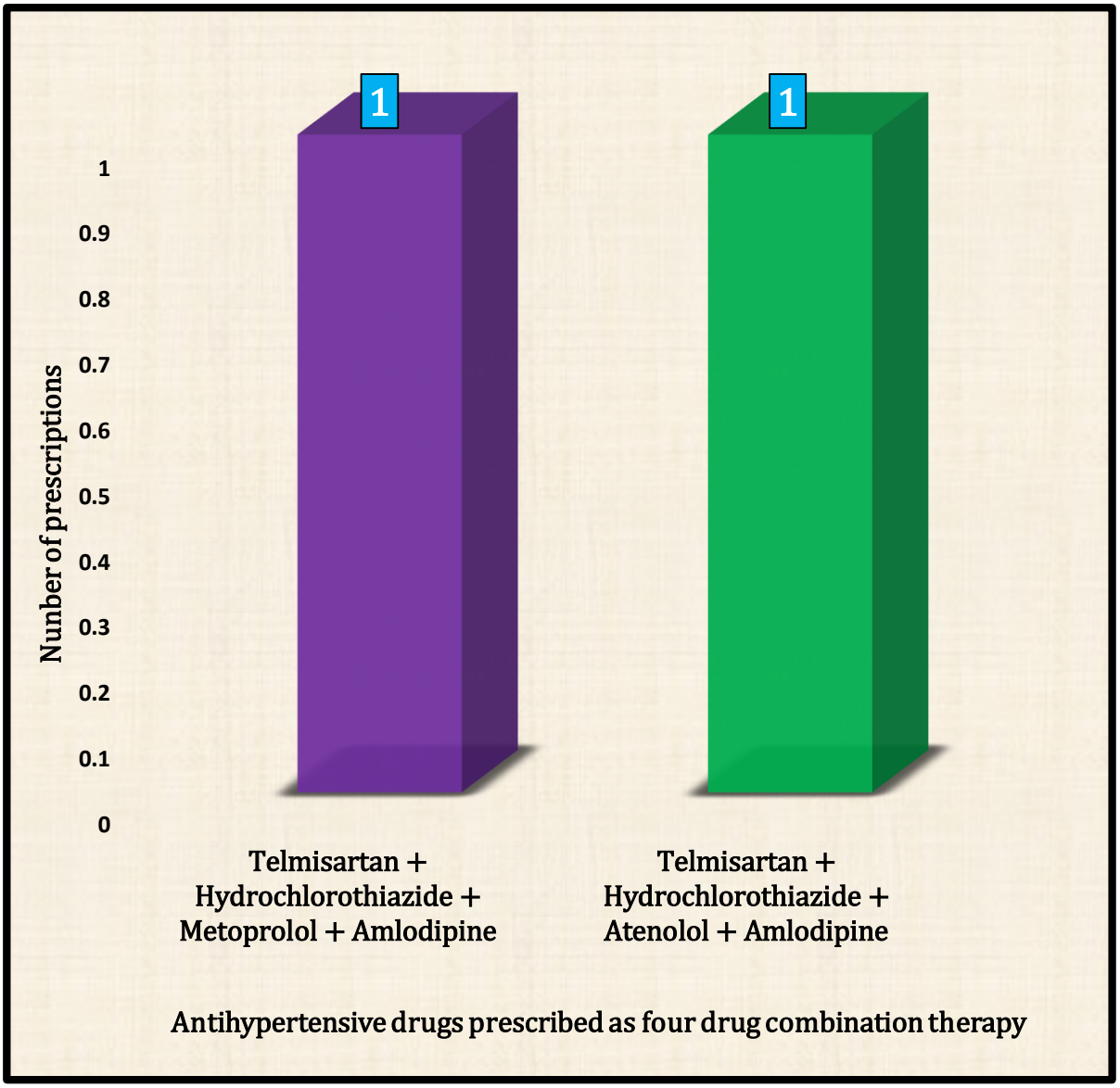

Figure 6. Bar diagram showing number of prescriptions of antihypertensive drugs as four drug combination therapy

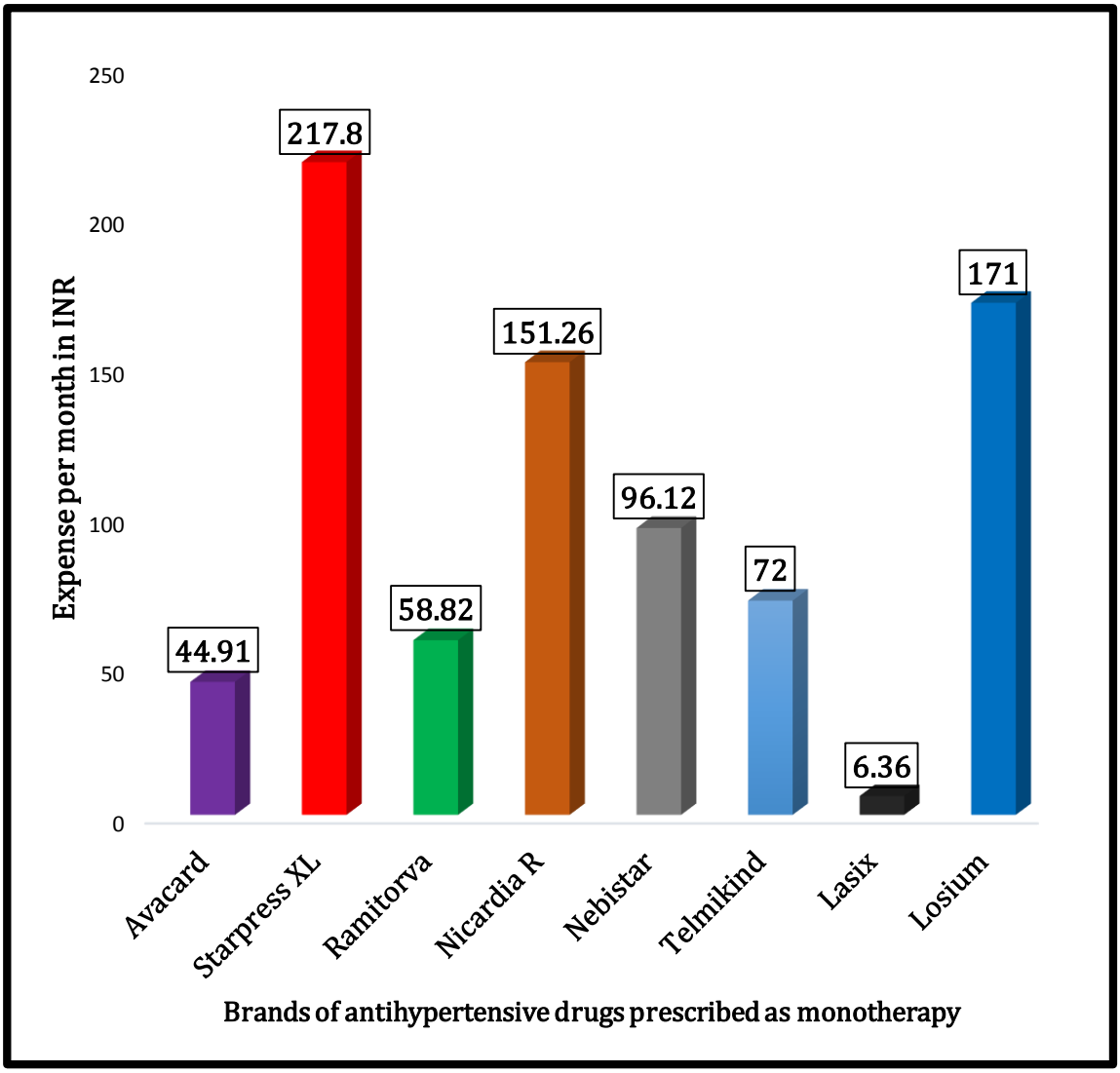

Figure 7. Bar diagram showing the expense per month of brands of antihypertensive drugs prescribed as monotherapy

Avacard : Amlodipine 5 mg OD
Starpress XL : Metoprolol 50 mg OD
Ramitorva : Ramipril 5 mg + Atorvastatin 10 mg + Aspirin 75 mg OD
Nicardia R : Nifedipine 20 mg OD
Nebistar : Nebivolol 2.5 mg OD
Telmikind : Telmisartan 40 mg OD
Lasix : Furosemide 20 mg OD
Losium : Losartan 50 mg OD
OD: Once daily **INR:** Indian rupee

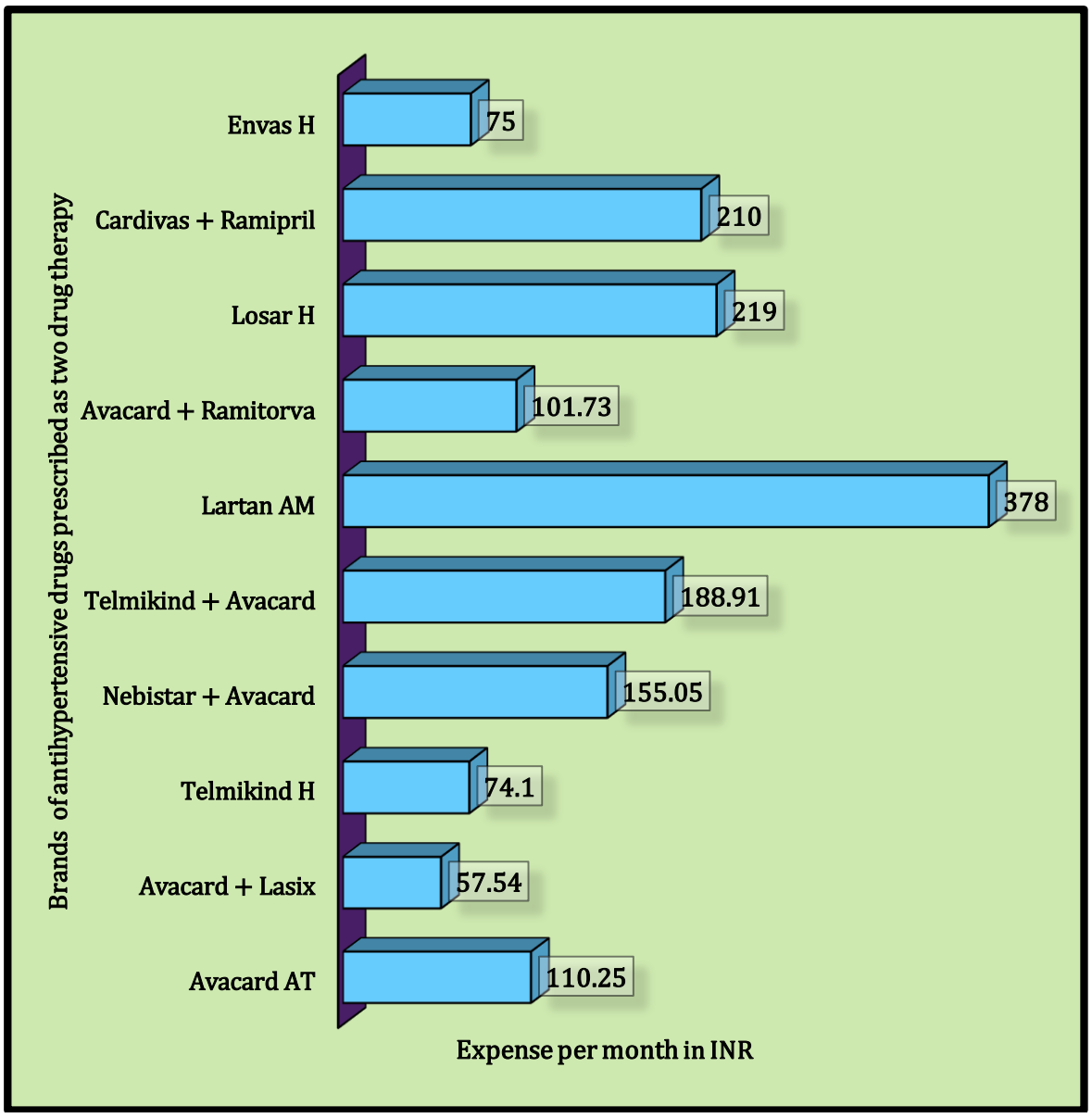

Figure 8. Bar diagram showing the expense per month of various brands of antihypertensive drugs prescribed as two drug therapy

Avacard AT	: Amlodipine 5 mg + Atenolol 50 mg OD
Avacard + Lasix	: Amlodipine 5 mg + Furosemide 40 mg OD
Telmikind H	: Telmisartan 40 mg + Hydrochlorothiazide 12.5 mg OD
Nebistar + Avacard	: Nebivolol 5 mg + Amlodipine 5 mg OD
Telmikind + Avacard	: Telmisartan 40 mg + Amlodipine 5 mg
Lartan AM	: Losartan 50 mg + Amlodipine 5 mg BD
Avacard + Ramitorva	: Amlodipine 5 mg OD, Ramipril 5 mg + Atorvastatin 10 mg + Aspirin 75 mg OD
Losar H	: Losartan 50 mg + Hydrochlorothiazide 12.5 mg OD
Cardivas + Ramipril	: Carvedilol 3.125 mg + Ramipril 2.5 mg OD
Envas H	: Enalapril 5 mg + Hydrochlorothiazide 12.5 mg OD

OD: Once daily **BD:** Twice daily **INR:** Indian rupee

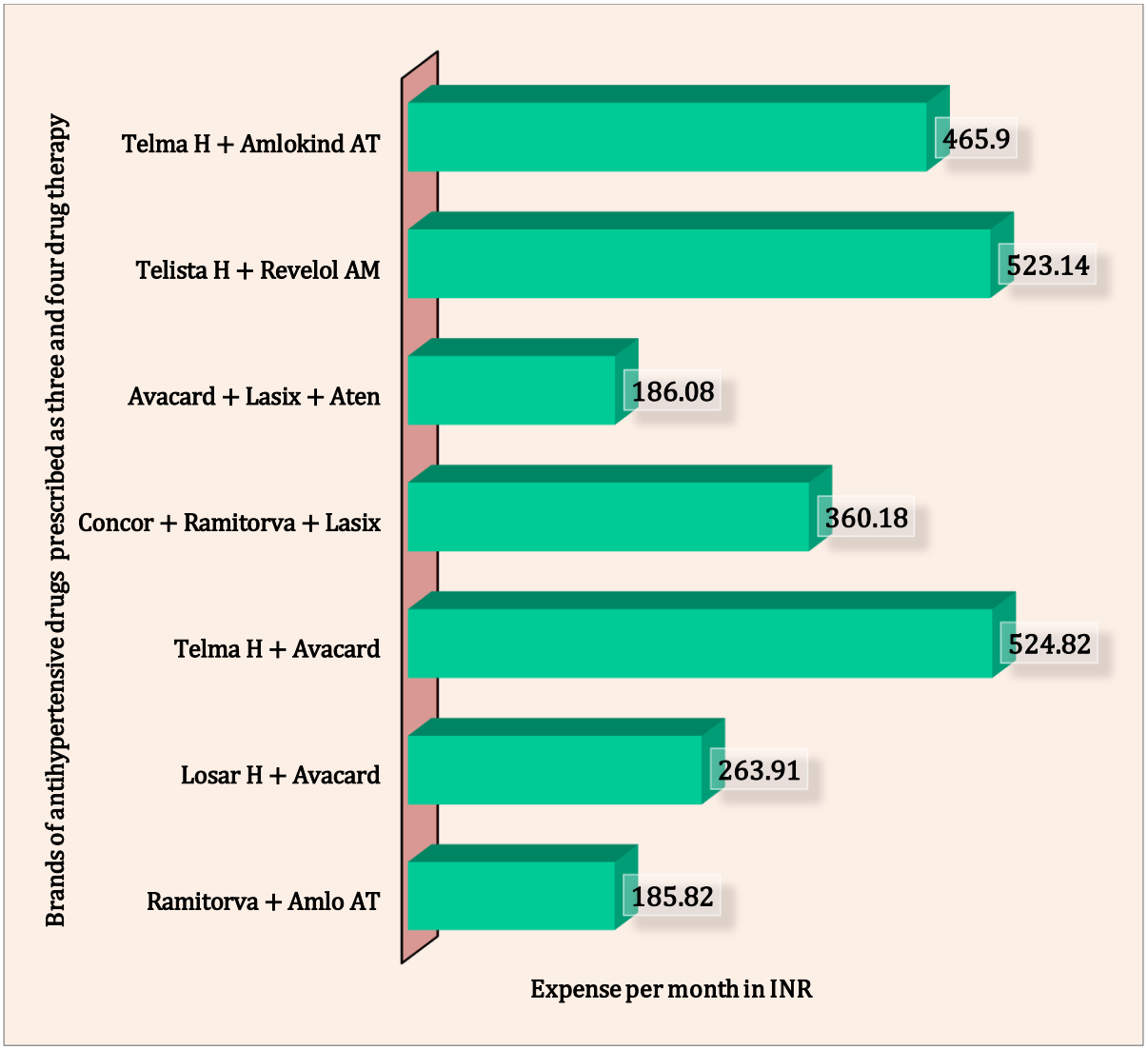

Figure 9. Bar diagram showing expense per month of various brands of antihypertensive drugs prescribed as three and four drug combination

Ramitorva + Amlo AT : Ramipril 5 mg + Atorvastatin 10 mg + Aspirin 75 mg OD, Amlodipine 5mg + Atenolol 50 mg OD

Losar H + Avacard : Losartan 50 mg + hydrochlorothiazide 12.5 mg OD, Amlodipine 5 mg OD

Telma H + Avacard : Telmisartan 40 mg+ Hydrochlorothiazide 12.5 mg OD, Amlodipine 5 mg BD

Concor + Ramitorva + Lasix : Bisoprolol 2.5 mg BD + Ramipril 5 mg + Atorvastatin 10 mg + Aspirin 75 mg OD, Furosemide 20 mg OD

Avacard + Lasix + Aten : Amlodipine 5 mg BD + Furosemide 40 mg BD + Atenolol 25 mg OD

Telista H + Revelol AM : Telmisartan 40 mg+ Hydrochlorothiazide 12.5 mg OD, Metoprolol 50 mg + Amlodipine 5 mg OD

Telma H + Amlokind AT : Telmisartan 40 mg+ Hydrochlorothiazide 12.5 mg OD, Atenolol 50 mg + Amlodipine 5 mg OD

OD: Once daily **BD:** Twice daily **INR:** Indian rupee

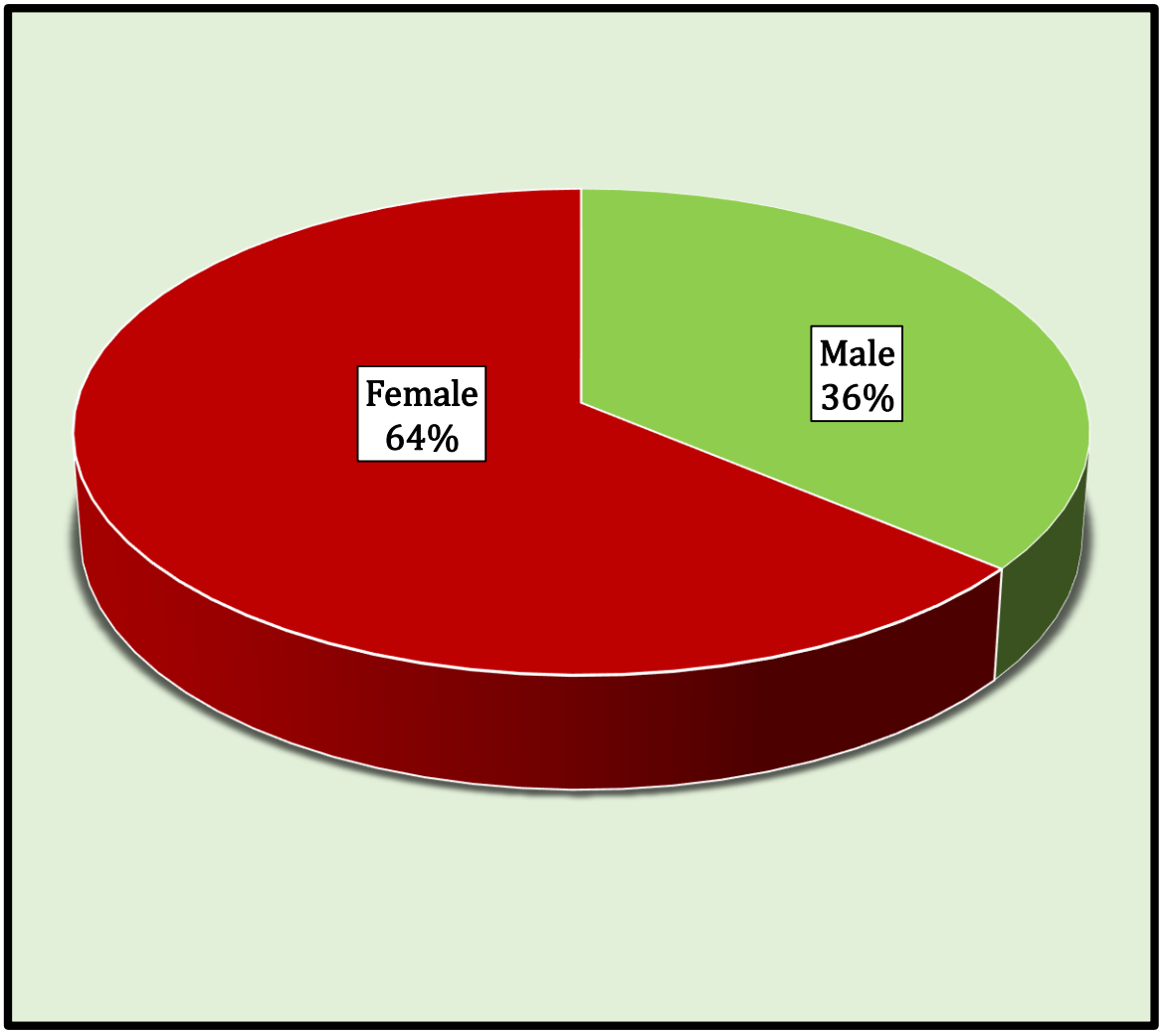

Figure 10. Pie diagram showing the percentage of males and females who experienced ADRs due to use of antihypertensive drugs

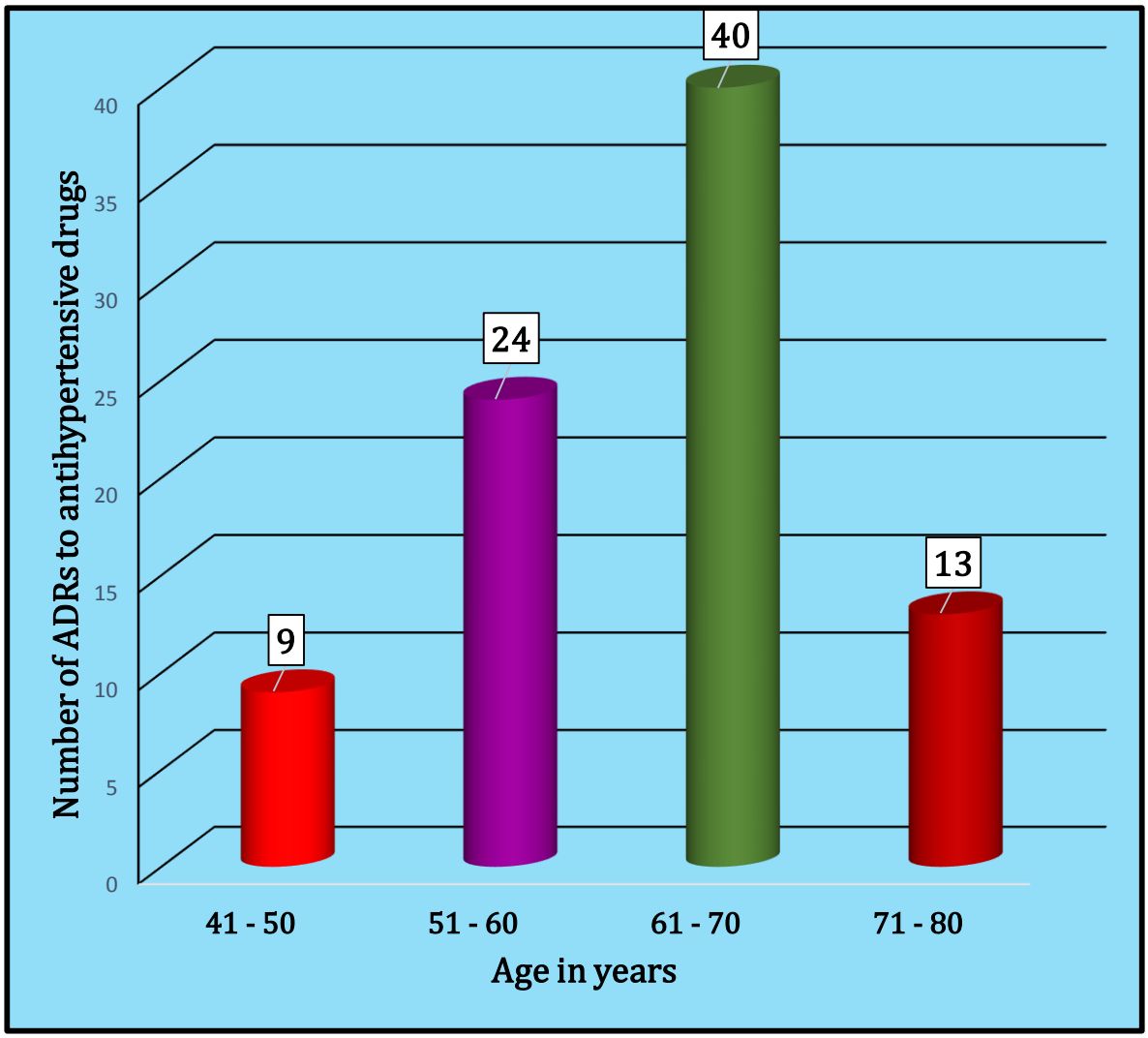

Figure 11. Bar diagram showing the age wise distribution of patients who experienced ADRs due to use of antihypertensive drugs

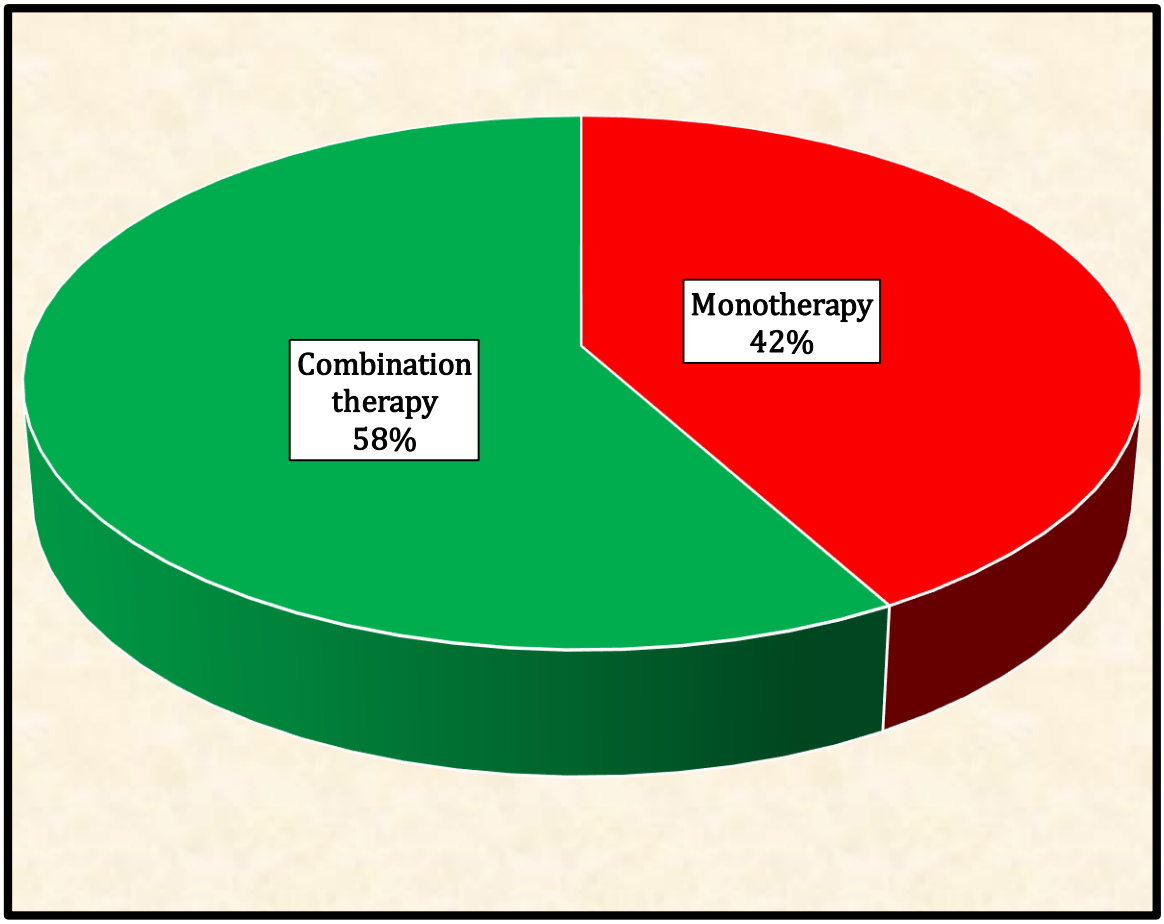

Figure 12. Pie diagram showing the percentage of ADRs experienced in patients who received monotherapy and combination therapy of antihypertensive drugs

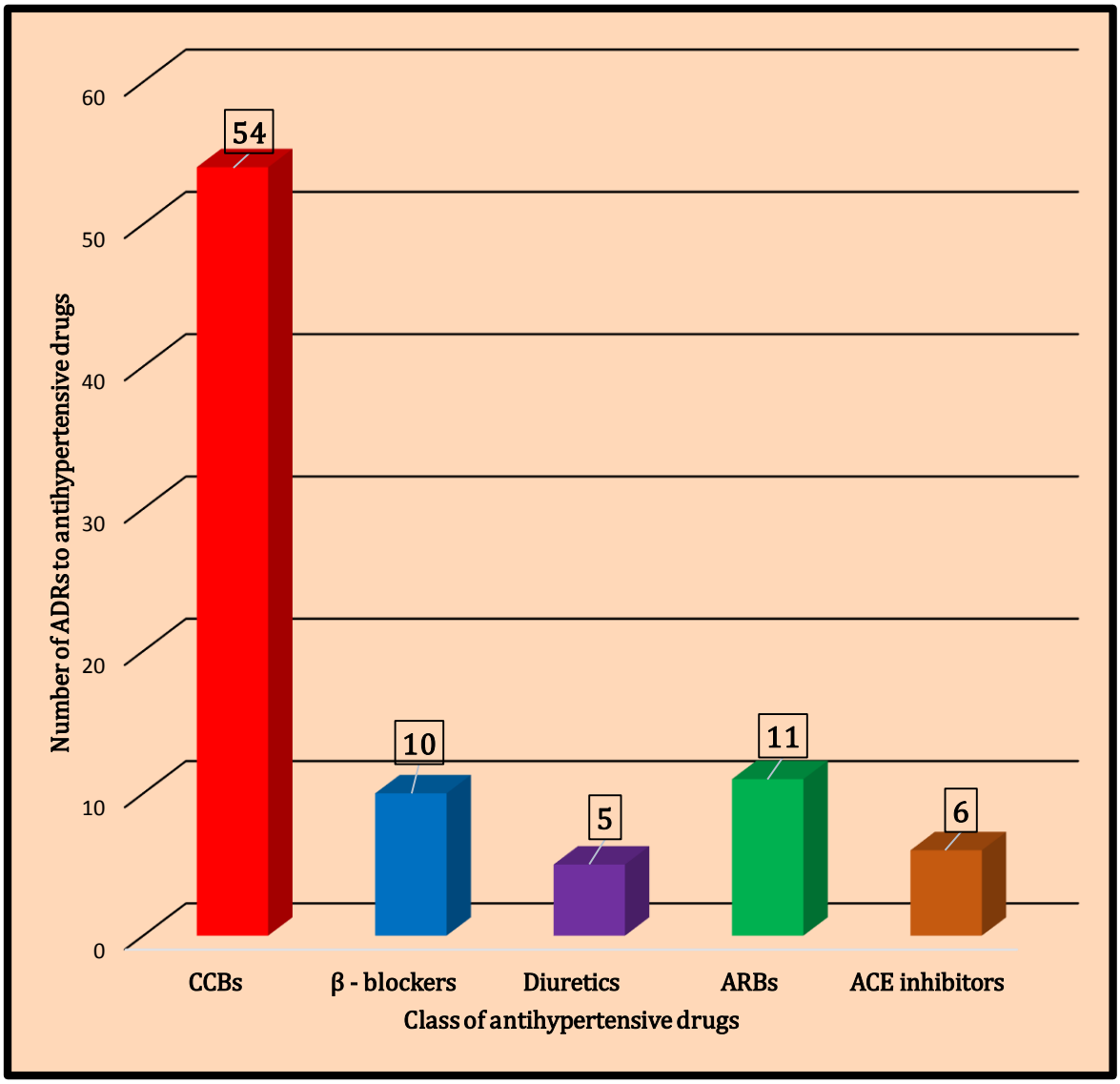

Figure 13. Bar diagram showing the number of ADRs experienced with different classes of antihypertensive drugs

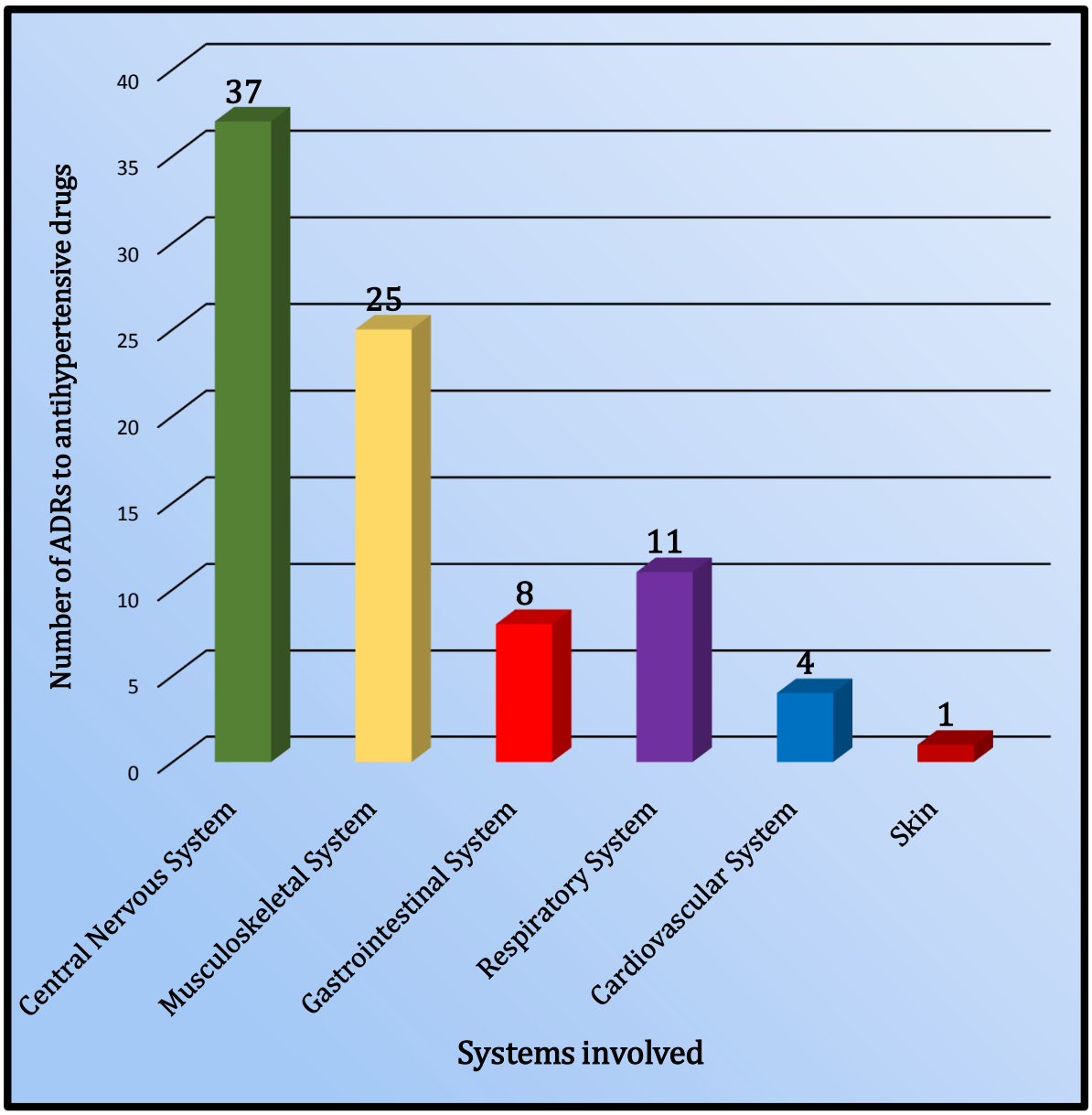

Figure 14. Bar diagram showing system-wise distribution of ADRs to antihypertensive drugs

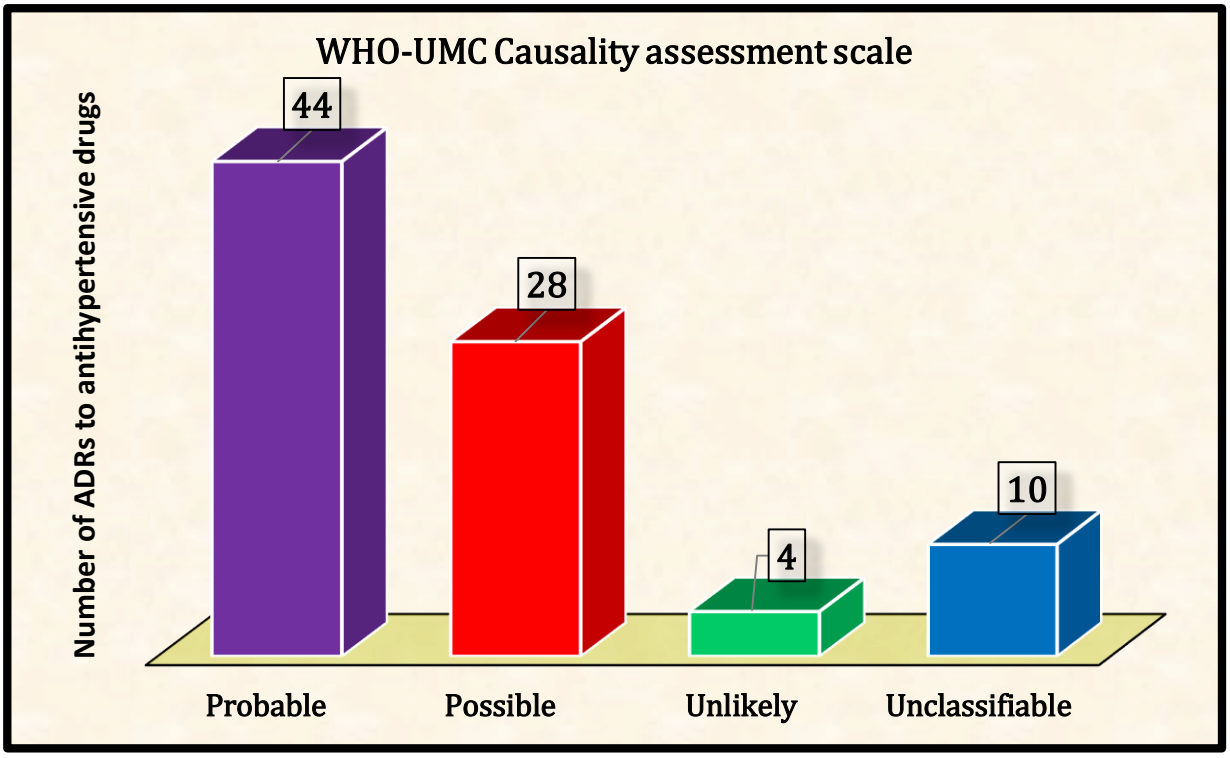

Figure 15. Bar diagram showing the causality assessment of ADRs due to antihypertensive drugs by WHO-UMC Causality assessment scale

WHO-UMC Causality Categories[26]

Certain

- Event or laboratory test abnormality, with plausible time relationship to drug intake
- Cannot be explained by disease or other drugs
- Response to withdrawal plausible
- Event definitive pharmacologically or phenomenologically
- Rechallenge satisfactory, if necessary

Probable/ Likely

- Event or laboratory test abnormality, with reasonable time relationship to drug intake
- Unlikely to be attributed to disease or other drugs
- Response to withdrawal clinically reasonable
- Rechallenge not required

Possible

- Event or laboratory test abnormality, with reasonable time relationship to drug intake
- Could also be explained by disease or other drugs
- Information on drug withdrawal may be lacking or unclear

Unlikely

- Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable
- Disease or other drugs provide plausible explanations

Conditional/ Unclassified

- Event or laboratory test abnormality
- More data for proper assessment needed, or
- Additional data under examination

Unassessable/ Unclassifiable

- Report suggesting an adverse reaction
- Cannot be judged because information is insufficient or contradictory
- Data cannot be supplemented or verified

WHO :World Health Organization

UMC :Uppsala Monitoring Centre

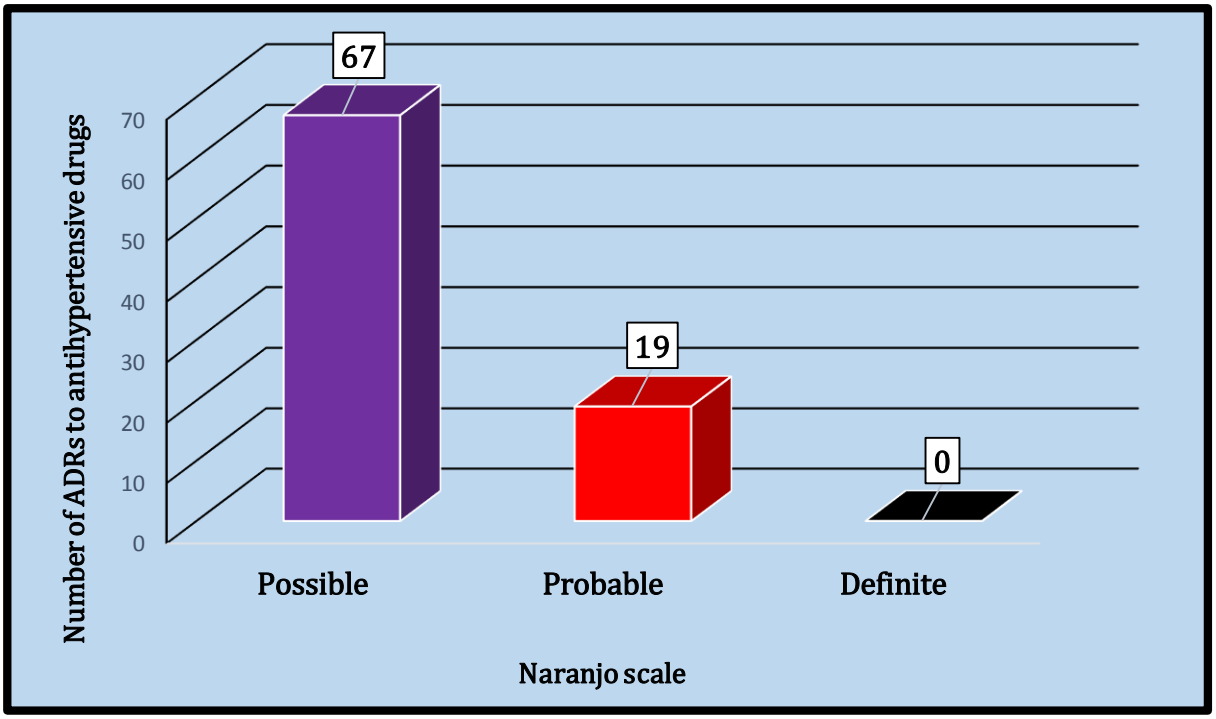

Figure 16. Bar diagram showing the causality assessment of ADRs due to antihypertensive drugs by Naranjo scale

Naranjo algorithm or adverse drug reaction probability scale[26] - The total score calculated from this table defines the category as: Possible (total score 1–4), Probable (total score 5–8), Definite (total score >9)

S.No.	Questionnaires	Yes	No	Do not know
1.	Are there previous conclusive reports on this reaction?	1	0	0
2.	Did adverse drug reaction (ADR) appear after the suspected drug was administered?	2	-1	0
3.	Did ADR improve when the drug was discontinued or a specific antagonist was administered?	1	0	0
4.	Did the adverse reaction appear when the drug was readministered?	2	-1	0
5.	Are there any alternative causes (other than the drug) that could have caused the reaction?	-1	2	0
6.	Did the reaction reappear when placebo was given?	-1	1	0
7.	Was the drug detected in the blood (or other fluids) in concentration known to be toxic?	1	0	0
8.	Was the ADR more severe when dose was increased or less severe when dose was decreased?	1	0	0
9.	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	1	0	0
10.	Was the adverse event confirmed by any objective evidence?	1	0	0

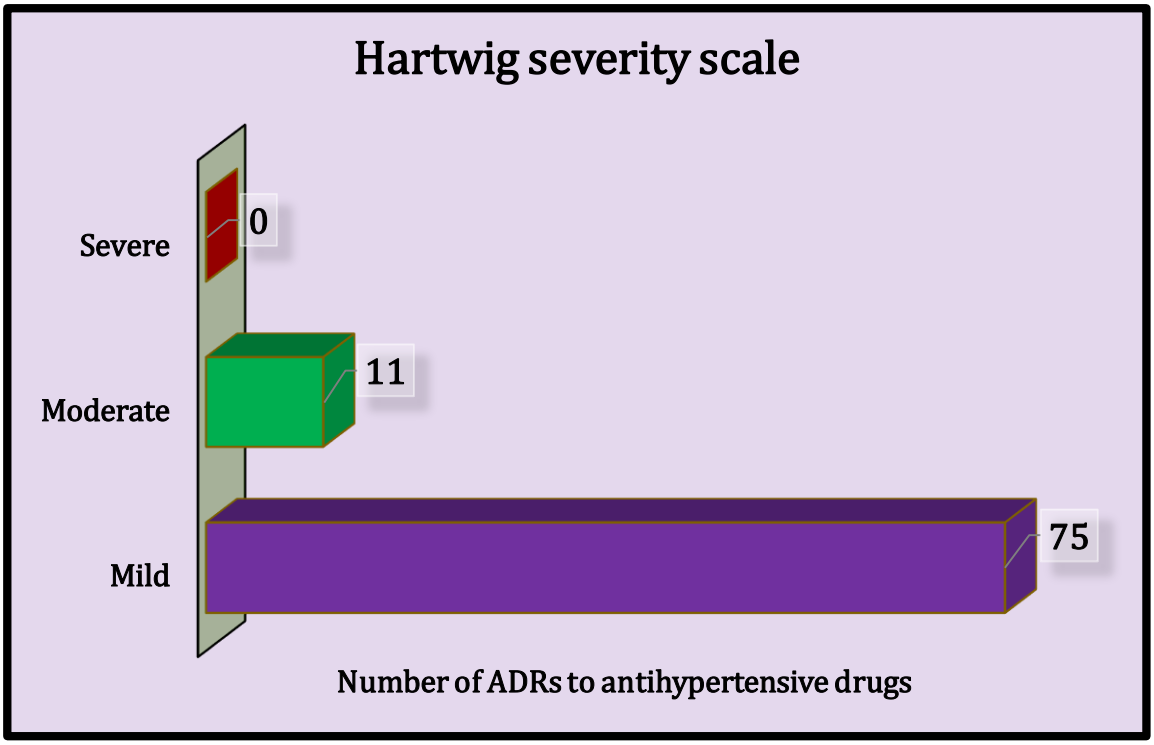

Figure 17. Bar diagram showing the severity assessment of ADRs due to antihypertensive drugs by Hartwig severity scale

Hartwig severity scale[28] - according to this scale ADRs were assessed as Mild (level 1, 2), Moderate (level 3, 4, 5) and Severe (level 6, 7)

Level 1	An ADR occurred but required no change in treatment with the suspected drug.
Level 2	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment requirement was required. No increase in length of stay.
Level 3	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. AND/OR An antidote or other treatment was required. No increase in length of stay.
Level 4	(A) Any level 3 ADR which increases length of stay by at least 1 day. OR (B) The ADR was the reason for the admission.
Level 5	Any level 4 ADR which requires intensive medical care.
Level 6	The adverse reaction caused permanent harm to the patient.
Level 7	The adverse reaction either directly or indirectly led to the death of the patient.

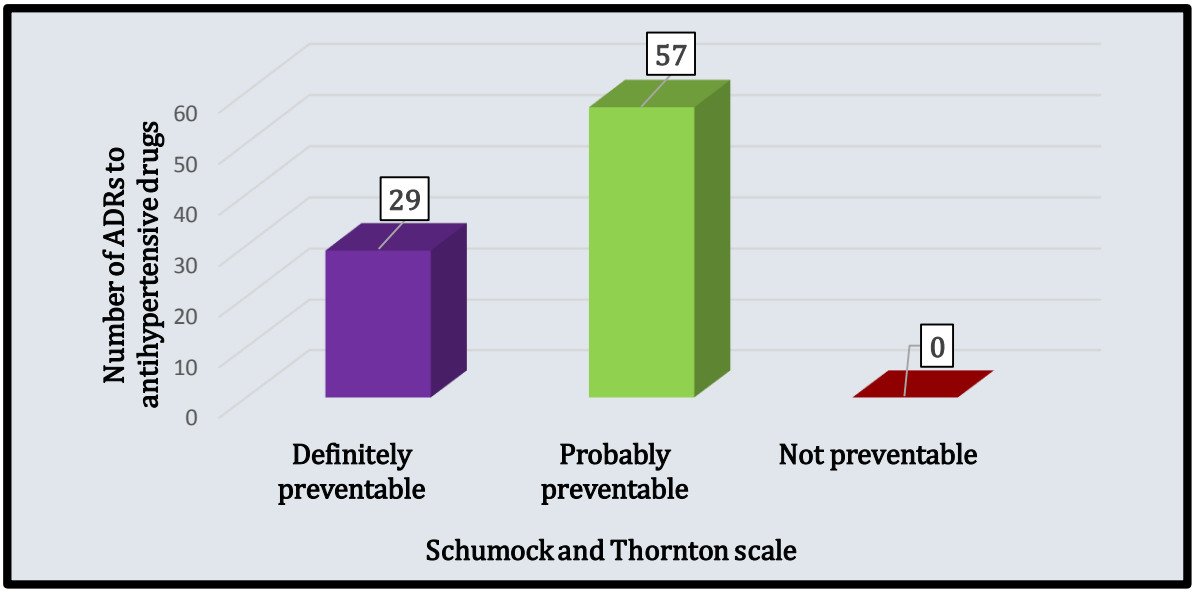

Figure 18. Bar diagram showing the preventability criteria of ADRs due to antihypertensive drugs by Schumock and Thornton scale.

Criteria for determining preventability of an adverse drug reaction (ADR) by modified Schumock and Thronton preventability scale[27]

SECTION A

Answering "yes" to one or more of the following implies that an ADR is DEFINITELY preventable.

1. Was there a history of allergy or previous reactions to the drug?
2. Was the drug involved inappropriate for the patient's clinical condition?
3. Was the dose, route, or frequency of administration inappropriate for the patient's age, weight, or disease state?

If answers are all negative to the above, then proceed to **Section B**

SECTION B

Answering "yes" to one or more of the following implies that an ADR is PROBABLY preventable

1. Was required therapeutic drug monitoring or other necessary laboratory tests not performed?
2. Was a documented drug interaction involved in the ADR?
3. Was poor compliance involved in the ADR?
4. Was a preventative measure not administered to the patient?
5. If a preventative measure was administered, was it inadequate and/or inappropriate?

Answer 'NO' if this question is nonapplicable.

If answers are all negative to the above, then proceed to **Section C**

SECTION C

The ADR is NOT preventable.

7. Discussion:

This study analysed the drug utilization pattern and ADR profile of antihypertensive drugs prescribed in the Department of Medicine, Sree Mookambika Institute of Medical Sciences, Kulasekharam, Tamilnadu.

In the present study 25.2% patients were male and 74.8% patients were female and this was similar to the study done by Khurshid et al.[8] In our study it was found that hypertension was more prevalent in females than males. There is comparatively less risk of hypertension in premenopausal women when compared to men.[56] Our study showed that common age group of patients with hypertension was 61 to 70 years but a study by Tiwari et al.[54] showed that the commonest age group affected was 50 to 60 years. Below 45 years of age men are more prone for hypertension but above 45 years women are more prone for hypertension.[18]

In our study 75.59% of the patients had received monotherapy of antihypertensive drug which was similar to the study by Bhradwaj et al.[64] and Pai et al.[52] but Etuk et al.[78] showed that two drug combinations are commonly prescribed. This difference is commonly due to the doctor's choice of treatment taking into consideration of various factors like patient characteristics, presence of any comorbid conditions and the medicine availability.[78]

In the present study amlodipine was the most commonly used drug as monotherapy in 87.5% of patients. CCBs have very less or no metabolic effects which is beneficial for diabetic hypertensive patients and also it is cheap. These could be the reasons for it to be the most commonly prescribed

drug. DUS of antihypertensive drugs by Maduram et al.[55] and John et al.[65] also showed amlodipine as the most frequently prescribed drug. The antihypertensive effect of CCBs are independent of sodium intake or concurrent use of NSAIDS which is not the case with ACE inhibitors. In patients having hypertension with coexisting nephropathy, CCBs remarkably reduce the blood pressure. CCBs are the most preferred drugs in case of hypertensive patients with coexisting diabetes mellitus. They also have additional natriuretic effect and thus it rules out the need for adding a diuretic.[17]

Present study found that amlodipine + atenolol was the most commonly prescribed two drug combination in 27.26% of patients which was similar to the study done by Joshi et al.[4] This could be because the efficacy of amlodipine is improved by combining it with β-blockers. By prescribing combination drugs, expenditure for the drugs can be minimized and also patient compliance may be improved.[18]

This study found that losartan + hydrochlorothiazide + amlodipine was the most commonly prescribed three drug combination in 42.84% of the patients but Kousalya et al.[79] showed enalapril + amlodipine + hydrochlorthiazide as the commonest three drug combination. In a study by Bhardwaj et al.[64] showed that none of the patient required three drug therapy.

The present study observed that monotherapy of antihypertensive drugs was more common than multiple drug therapy. But Janagan et al.[56] showed that combination therapy was more common than monotherapy.

Diuretics are the first line drugs in treatment of hypertension according to JNC 7[80] guidelines. But NICE guidelines[81] on the management of primary hypertension in adults recommends ACE inhibitor or ARB as initial treatment of hypertension under 55 years. But if patients are more than 55 years then CCBs are used as first line drugs. Diuretics should be used as first choice drugs only if CCBs are contraindicated in the patient or if the patient has developed oedema or if patient is at risk of developing heart failure. In our study CCB was the most commonly used drug and diuretic was prescribed less frequently.

In this study all the antihypertensive drugs were prescribed by brand name and none by generic name which is not a good indicator of rational prescription. Provision of drugs in their generic name, prescribing from EDL and rational drug prescribing of drugs are recognized measures that can considerably reduce the expenditure for drugs to patients. In this way treatment standard will be maintained and will help to attain optimal control of hypertension. Prescriptions by brand name will help to reduce the drug expenses and will also rationalise prescriptions.[82]

One of the important factors which affects patient compliance and drug adherence is the occurrence of adverse drug reactions. In the present study, out of 86 ADRs recorded, 63.95% were female and 36.05% were male. Theoretically women were thought to be at greater risk of adverse drug reactions than men, which might be due to gender related differences in pharmacokinetics, immunology and hormonal factors. Rational adjustment of dose will help to minimise ADRs in females.

In our study, ADRs were found to be more common in age group of 61 to 70 years which was similar to the study by Solanki et al.[19] It was found that elderly patients are more prone to ADRs than younger patients.

In our study most common system associated with ADRs was central nervous system; but Hussain et al.[67] study reported cardiovascular system as the commonly affected system. In our study ADRs also involved musculo-skeletal system, respiratory system, gastrointestinal system, cardiovascular system and skin. This study showed that different patterns of prescriptions of antihypertensive drugs produced different types of ADRs.

As anticipated, patients who received combination therapy were associated with more number of ADRs (58.14%) as compared to patients who were on monotherapy (41.86%). Use of multiple drugs in hypertension should be avoided as there are higher chances of developing ADRs and it may also cause drug interactions. Only the absolutely essential medicines should be prescribed for treatment of hypertension.

In the current study, CCBs were the common group of antihypertensive drugs associated with ADRs (62.79%) which was similar to the study by Basak et al.[76] In CCBs, amlodipine was found to be the commonest drug associated with ADRs. The most common individual ADR was headache which was seen in 20.93% of the patients which was similar to the study done by Alomar et al.[74] This could be due to arteriolar vasodilatation caused by CCBs. CCBs are also not suitable in patients with left ventricular dysfunction due to their negative inotropic effect.[18] In our study peripheral oedema is also one of the common ADR seen with the use of CCBs. It occurs due to precapillary dilation

and reflex post capillary constriction causing increase in hydrostatic pressure.[18]

Our study showed that according to WHO causality assessment scale 51.16% of the ADRs were probable which means that these reactions are caused by the use of antihypertensive drugs and not due to any disease or by the use of other drugs and clinical improvement is seen when the drug is dechallenged. Possible ADRs were seen in 32.56% of the patients which could be due to presence of a disease or simultaneous use of other drugs.

The causality assessment by Naranjo scale showed that 77.91% ADRs were Possible. Naranjo scale helps to determine whether ADR is due to the drug or due to other factors. A study done by Rende et al.[72] showed a probable association in 92% and a possible association in 8%.

In our study Modified Hartwig and Siegel's scale was used to assess the severity of ADRs. According to this scale 87.21% of ADRs were mild and this was in accordance with the study done by Hussain et al.[67]

In the present study Modified Schumock and Thornton scale was used to assess the preventability of ADRs and it was found that 66.28% of ADRs were definitely preventable but Haile et al.[83] In his study showed that majority of the ADRs were probably preventable. Our study showed that elderly individuals were at high risk of developing ADRs and most of the ADRs were preventable. Prescribing doctors should have sound knowledge regarding the basic pharmacology and how age affects pharmacokinetics of the drugs which will help to prevent various ADRs.

8. Conclusion:

In a cross-sectional study conducted in this institute during the period from October 2013 to March 2014 to evaluate the drug utilization pattern of antihypertensive drugs it was seen that 75.59% of drug prescriptions were by monotherapy and 24.41% by combination therapy and all the prescriptions were found to be rational. The study also showed that all the prescriptions were by brand name. The pharmacoeconomics of the antihypertensive drugs prescribed in the study revealed furosemide as the least expensive and metoprolol as the most expensive drugs prescribed as monotherapy. In the combination therapy the least expensive was amlodipine with furosemide and most expensive was the combinations of telmisartan, hydrochlorothiazide and amlodipine.

In this study the ADRs were found probable (51.16%), possible (32.56%), unclassifiable (11.63%) and unlikely (4.65%) by using WHO causality assessment scale. By using Naranjo algorithm scale it was found that ADRs were possible in 77.91% and probable in 22.09% of cases. Modified Schumock and Thornton scale for preventability of ADRs showed that ADRs were definitely preventable in 33.72% and probably preventable in 66.28% of cases. Modified Hartwig and Siegel scale for severity of ADRs showed that 87.21% of the ADRs reported were mild and 12.79% were moderate. This study also found that amlodipine was responsible for most of the ADRs and among all the ADRs reported headache was the commonest followed by dizziness, pedal oedema, fatigue, abdominal pain, dry cough, breathlessness, bradycardia, muscle cramps, sedation, diarrhoea and irritation all over the body.

9. Summary:

The present cross-sectional study was undertaken to study the drug utilization pattern in patients with hypertension and to analyse the adverse drug reaction profile of antihypertensive drugs. The study was conducted for a period of 6 months. The data was collected using a case record form. The study included patients of all age group.

A total of 127 prescriptions of patients receiving antihypertensive drugs from Medicine department were collected. Commonest age group of the patients was 61-70 years. The incidence of hypertension in females (74.8%) was found to be more than males (25.2%). All the antihypertensive drugs were prescribed by brand name. Monotherapy (75.59%) was preferred more than combination therapy (24.41%). Amlodipine was the most commonly prescribed drug as monotherapy. Amlodipine with atenolol was the most commonly prescribed combination therapy. Metoprolol was the most expensive and furosemide was the least expensive drug prescribed as monotherapy. Telmisartan with hydrochlorothiazide and amlodipine was the most expensive and amlodipine with furosemide was the least expensive drugs prescribed as combination therapy. The overall analysis of the prescription patterns is suggestive of rational prescribing practices in the selection of suitable antihypertensive drugs.

A total of 86 ADRs to antihypertensive drugs were also collected during the study period. Majority of the ADRs were in females (63.95%) followed by males (36.05%). Most common age group affected by ADRs was 61-70 years. Patients receiving combination therapy (58.14%) of antihypertensive drugs

were more frequently associated by ADRs than patients on monotherapy (41.86%). CCBs was found to be the most common class of antihypertensive drugs associated with ADRs. Most common system associated with ADRs was central nervous system. Headache was the most common individual ADR followed by dizziness, pedal oedema, fatigue, abdominal pain, dry cough, breathlessness, bradycardia, muscle cramp, sedation, diarrhoea and irritation all over the body.

10. References:

1. Halemani SS, Narendranth S, Somashekhar HS, Reshma SR, Sagar JK, Ramachandra K. Prescriptive pattern of antihypertensives in tertiary care hospital using DU-90%. Int J Pharm Res Dev 2012;4(1):107-13.
2. Kalamdani AR, Bhandare B, Hemamalini MB, Krishna MV. A prospective study of prescribing pattern of antihypertensive drugs in tertiary care hospital, Bangalore. J Evol Med Dent Sci 2014;2(52):10339-44.
3. Mohd AH, Mateti UV, Konuru V, Parmar MY, Kunduru BR. A study on prescribing patterns of antihypertensives in geriatric patients. Perspect Clin Res 2012;3(4):139-42.
4. Joshi M, Rao BS, Khan GM. Study of drug use in essential hypertension and their compliance. Kathmandu Univ J Sci Eng Technol 2006;2(1):1-13.
5. Lee PKF, Li RKL, Chan JCN, Chang S, Lee SC, Tomlinson B, Critchley JAJH. A prescription survey in a hospital hypertension outpatient clinic. Br J Clin Pharmacol 1997;44(6):577–82.
6. Al-Windi A. Detection and treatment of hypertension in general health-care practice: a patient-based study. J Hum Hypertens 2005;19(10):775-86.
7. Rimoy GH, Justin-Temu M, Nilay C. Prescribing patterns and cost of antihypertensive drugs in private hospitals in Dar es Salaam, Tanzania. East Cent Afr J Pharm Sci 2008;11(3):69-73.
8. Khurshid F, Aqil M, Alam MS, Kapur P, Pillai KK. Antihypertensive medication prescribing patterns in a university teaching hospital in South Delhi. Int J Pharm Sci Res 2012;3(7):2057-63.
9. Kumar VR, Ram VR, Prasad BG, Mohanta GP, Manna PK. A study of adverse drug reactions due to antihypertensive drugs in a tertiary care teaching hospital. Int J Pharm Life Sci 2011;2(5):767-72.
10. Khurshid F, Aqil M, Alam MS, Kapur P, Pillai KK. Monitoring of adverse drug reactions associated with antihypertensive medicines at a university teaching hospital in New Delhi. DARU J Pharm Sci 2012;20(1):1-6.
11. Ahmad SR. Adverse drug event monitoring at the food and drug administration. J Gen Intern Med 2003;18(1):57-60.
12. Park K. Park's Textbook of Preventive and Social Medicine. 22nd ed. Jabalpur: Banarsidas Bhanot; 2013. p. 344-8.
13. Esunge PM. From blood pressure to hypertension: the history of research. J R Soc Med 1991;84(10):621.
14. Newby DE, Grubb NR, Bradbury A. Vascular disease. Walker BR, Colledge NR, Ralston SH, Penman ID editors. Davidson's Principles and Practice of Medicine. 22nd ed. Edinburgh: Churchill Livingstone; 2014. p. 607-13.
15. Kotchen TA. Hypertensive Vascular Disease. Longo DL, Fauci A, Kasper D, Hauser S, Jameson JJ, Loscalzo J editors. Harrison's Principles of Internal Medicine. 18th ed. New York: McGraw-Hill; 2011. p. 4139-65.

16. Benowitz NL. Antihypertensive Agents. Katzung BG, Masters SB, Trevor AJ editors. Basic and Clinical Pharmacology. 12th ed. New York: McGraw-Hill; 2012. p. 169-92.
17. Michel T, Hoffman BB. Treatment of Myocardial Ischemia and Hypertension. Brunton L, Chabner BA, Knollman B editors. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th ed. New York: McGraw-Hill; 2011. p. 765-85.
18. Tripathi KD. Essentials of Medical Pharmacology. 7th ed. New Delhi: Jaypee; 2013. p. 558-74.
19. Solanki KC, Mistry RA, Singh AP, Jadav SP, Patel NM, Trivedi HR. Drug utilization study of antihypertensive drugs and their adverse effects in patients of a tertiary care hospital. J Clin Exp Res 2013;1(3):58-67.
20. Shalini S, Ravichandran V, Mohanty BK, Dhanaraj SK, Saraswathi R. Drug utilization studies – an overview. Int J Pharm Sci Nanotechnol 2010;3(1):803-10.
21. Souich PD, Orme M. The IUPHAR Compendium of Basic Principles for Pharmacological Research in Humans. Irvine: IUPHAR; 2004.p. 76-86.
22. Truter I. A review of drug utilization studies and methodologies. Jordan J Pharm Sci 2008;1(2):91-104.
23. Sachdeva PD, Patel BG. Drug utilization studies-scope and future perspectives. Int J Pharm Biol Res 2010;1(1):11-7.
24. Patel A, Giles D, Thomas V, Gurubasavarajaswamy PM, Patel R. Pharmacovigilance: a review. Int J Pharm Biol Arch 2011;2(6):1569-74.
25. Rohilla A, Singh N, Kumar V, Sharma MK, Dahiya A, Kushnoor A. Pharmacovigilance: needs and objectives. J Adv Pharm Edu Res 2012;2(4):201-5.
26. Zaki SA. Adverse drug reaction and causality assessment scales. Lung India 2011;28(2):152-3.
27. Raut AL, Patel P, Patel C, Pawar A. Preventability, predictability and seriousness of adverse drug reactions amongst medicine inpatients in a teaching hospital: a prospective observational study. Int J Pharm Chem Sci 2012;1(3):1293-9.
28. Srinivasan R, Ramya G. Adverse drug reaction-causality assessment. Int J Res Pharm Chem 2011;1(3):606-12.
29. Augustine L, Prasanth NV, Dev KTS, Jasmin S, Kappekkat Y, Shinu C, Thayyil A. A study conducted on prescribing pattern and cost of anti-hypertensive drugs in a tertiary level hospital in South Malabar region of Kerala. Der Pharma Chemica 2010;2(6):332-41.
30. Beg MA, Dutta S, Varma A, Kant R, Bawa S, Anjoom M. Study on drug prescribing pattern in hypertensive patients in a tertiary care teaching hospital at Dehradun, Uttarakhand. Int J Med Sci Public Health 2014;3(8):1-5.
31. Tandon VR, Sharma S, Mahajan S, Mahajan A, Khajuria V, Mahajan V, Prakash C. Antihypertensive drug prescription patterns, rationality, and adherence to Joint National Committee-7 hypertension treatment guidelines among Indian postmenopausal women. J Mid-life Health 2014;5(2):78-83.
32. McAlister FA, Campbell NR, Duong-Hua M, Chen Z, Tu K. Antihypertensive medication prescribing in 27,822 elderly Canadians with diabetes over the past decade. Diabetes Care 2006;29(4):836-41.

33. Liu P, Wang J. Antihypertensive medication prescription patterns and time trends for newly-diagnosed uncomplicated hypertension patients in Taiwan. BMC Health Serv Res 2008;8:1-11.
34. Yoon EY, Cohn L, Rocchini A, Kershaw D, Freed G, Ascione F, Clark S. Antihypertensive prescribing patterns for adolescents with primary hypertension. Pediatr 2012;129(1):1-8.
35. Gupta SK, Nayak RP. The pattern of antihypertensive medication use among elderly patients in a tertiary care teaching hospital in South India. Trop J Med Res 2014;17(2):81-5.
36. Sakthi RS, Thomas S, Sivakumar KK, Karhikeyan J, Kumar NS. Assessment of antihypertensive prescribing pattern and patient counseling in an urban population. Der Pharmacia Lettre 2010;2(4):156-63.
37. Kehinde AG, Ismail AS. Assessment of antihypertensives utilization in a private teaching hospital in Nigeria. Int J Pharm Pharm Sci 2012;4(5):480-3.
38. Sultana S, Hamid K, Islam KMS, Roy S, Saha MR, Zulfiker AHM et al. Assessment of prescription pattern of hypertensive patient's prescription: A prescription survey study from various hospitals of Bangladesh. Eur J Sci Res 2010;40(4):500-5.
39. Clement YN, Ali S, Harripaulsingh S, Lacaille K, Mohammed O, Mohammed S et al. Drug prescribing for hypertension at primary healthcare facilities in Trinidad. West Indian Med J 2012;61(1):43-8.
40. Janaki RT, Narendra.SH. Drug prescription pattern of antihypertensive drugs in a tertiary hospital. J Pharm Biomed Sci 2009;9(9):1-5.
41. Baig MR, Yuit WS, Ramani M, Jin PC, Asma M, Tahir MK. Drug utilization pattern and co-morbidtities among hypertensive patients in sub-urban hospital, Malaysia. Rev Global Med Healthcare Res 2011;2(2):139-46.
42. Hooli TV, Santoshkumar J, Manjunath S, Vinodkumar CS. Drug utilization study of antihypertensives in obstetric practice in a tertiary care hospital. Int J Appl Biol Pharm Technol 2010;1(3):1006-10.
43. Azarisman SMS, Aszrin A, Sahimi M, Ngow HA, Marzuki AO, Jamalludin AR, Sapari S, Maskon O. Evaluation of antihypertensive drug utilisation and cost in Hospital Tengku Ampuan Afzan, Kuantan. Int Med J 2009;8(2):29-36.
44. Arief M, Harika B, Satyanarayana B, Pasha SW, Paladugu ND, Pasha SI, Poloju D, Pokkula S. Evaluation of prescribing pattern of antihypertensive drugs in a tertiary care hospital. Acta Chim Pharm Indica 2013;3(2):172-81.
45. Ghori SAU, Baig MMA, Ilyaz M, Areif M, Tabassum N. Evaluation of prescribing pattern of antihypertensives against the clinical condition. J Pharm Biol Sci 2014;9(2):133-40.
46. Xavier D, Mathew N, Pradeep J, Pais P. Pattern of drug use in hypertension in a tertiary hospital: A cross sectional study in the in-patient wards. Indian J Pharmacol 2001;33(6):456-7.
47. Majumder AAS. Patterns of antihypertensive drug utilization among the cardiologists of Bangladesh in initiating hypertension treatment. Cardiovasc J 2012;4(2):114-9.

48. Pittrow D, Kirch W, Bramlage P, Lehnert H, Hofler M, Unger T, Sharma AM, Wittchen HU. Patterns of antihypertensive drug utilization in primary care. Eur J Clin Pharmacol 2004;60(2):135–42.
49. Wong MC, Jiang JY, Lam AT, Fung H, Griffiths S, Mercer SW. Patterns of antihypertensive prescribing, discontinuation and switching among a Hong Kong Chinese population from over one million prescriptions. J Hum Hypertens 2008;22(10):714-6.
50. Sweileh W. Pharmacotherapeutic Analysis and prescription pattern of antihypertensive drugs dispensed at community pharmacies in Palestine. An-Najah Univ J Res 2003;17(2):168-81.
51. Sagar JK, Narendranath S, Somashekar HS, Reshma SR, Halemani SS, Adake P. Prescribing pattern of antihypertensives in individuals with hypertension alone and with coexisting diabetes mellitus - a comparative study. Int J Cur Biomed Phar Res 2012;2(2):300- 3.
52. Pai PG, Shenoy J, Sanji N. Prescribing patterns of antihypertensive drugs in a South Indian tertiary care hospital. Drug Invention Today 2011;3(4):38-40.
53. Kale A, Maniyar YA. Prescribing patterns of antihypertensive drugs in a tertiary care hospital. Sch Acad J Pharm 2013;2(5):416-8.
54. Tiwari H, Kumar A, Kulkarni SK. Prescription monitoring of antihypertensive drug utilisation at the Panjab university health centre in India. Singapore Med J 2004;45(3):117-20.
55. Maduram A, Harikrishna. Prescription pattern of antihypertensive drugs in Shri Sathya Sai medical college & research institute. Int J Basic Med Sci 2013;4(2):68-72.
56. Janagan T, Kavitha R, Sridevi SA, Veerendra V. Prescription pattern of antihypertensive drugs used in hypertensive patients with associated type 2 diabetes mellitus in a tertiary care hospital. Int J Pharm Res Rev 2014;3(1):1-5.
57. Dhanaraj E, Raval A, Yadav R, Bhansali A, Tiwari P. Prescription pattern of antihypertensive agents in T2DM patients visiting tertiary care centre in North India. Int J Hypertens 2012:520915.
58. Al-Drabah E, Irshaid Y, Yasein N, Zmeili S. Prescription pattern of antihypertensive drugs in family practice clinics at Jordan University Hospital. Med Sci 2012;2(1):469-88.
59. Bajaj JK, Sood M, Singh SJ, Jerath P. Prescription patterns of antihypertensive drugs and adherence to JNC VII guidelines in a tertiary care hospital in North India. Int J Med Clin Res 2012;3(2):118-20.
60. Pavani V, Cidda M, Krishna TR, Parmar MY, Nalini M. Study of prescribing patterns of antihypertensive drugs. Int J Pharm Bio Sci 2012;2(2):317-27.
61. Shah J, Khakhkhar T, Bhirud S, Shah RB, Date S. Study of utilization pattern of antihypertensive drugs in hypertensive diabetic patients with or without reduced renal function at tertiary care teaching hospital. Int J Med Sci Public Health 2013;2:167-72.
62. Sindhu PR, Reddy MS. Study of prescriptive patterns of antihypertensive drugs in South India. Int J Adv Res Technol 2013;2(6):295-311.

63. Sandozi T, Emani VK. Survey of prescription pattern of antihypertensive drugs in hypertensives and hypertension associated diabetics. Int J Pharm Biosci 2010;1(4):23-6.
64. Bhardwaj A, Alam N, Dabas V, Tiwari R, Sharma S. To evaluate the drug utilization pattern in patients using antihypertensive drug therapy. Asian J Biochem Pharm Res 2012;2(1):425-33.
65. John LJ, Devi P, Guido S. Utilization of antihypertensive medications among the critically ill patients. Res J Pharm Biol Chem Sci 2012;3(3):650-4.
66. Fretheim A, Oxman AD. International variation in prescribing antihypertensive drugs: its extent and possible explanations. BMC Health Serv Res 2005;5(1):21.
67. Hussain A, Aqil M, Alam MS, Khan MR, Kapur P, Pillai KK. A pharmacovigilance study of antihypertensive medicines at a South delhi hospital. Indian J Pharm Sci 2009;71(3):338-41.
68. Joshi VD, Dahake AP, Suthar AP. Adverse effects associated with the use of antihypertensive drugs: An overview. Int J Pharm Tech Res 2010;2(1):10-3.
69. Kale S, Patil A, Mandlecha RH. Compliance and adverse drug effects of antihypertensives in rural India. J Clin Diagn Res 2011;5(4):775-9.
70. Upadhayai JB, Kumar NA, Mukhija RD, Mukum M, Lalit M, Singh KK. Cutaneous reactions due to antihypertensive drugs. Indian J Dermatol 2006;51(3):189-91.
71. Minto-Leon D, Reyes-Morales, Galvan-Plata ME, Ponce-Monter H, Palma-Aguirre JA, Amato D, Figueras A. Drug treatment of hypertension: Compliance and adverse reactions in a cohort of hypertensive patients in a primary care setting. Rev Invest Clin 2007;59(1):8-14.
72. Rende P, Paletta L, Gallelli G, Raffaele G, Natale V, Brissa N, Costa C, Gratteri S, Giofre C, Gallelli L. Retrospective evaluation of adverse drug reactions induced by antihypertensive treatment. J Pharmacol Pharmacother 2013;4(1):47-50.
73. Suhas D, Bhosle D, Atre K. Review on pharmacovigilance study of telmisartan in hypertension patients. Asian J Pharm Clin Res 2013;6(3):17-20.
74. Alomar MJ, Strauch CC. A prospective evaluation of antihypertensive medications safety and efficacy in United Arab Emirates private hospitals. Am J Pharmacol Toxicol 2010;5(2):89-94.
75. Ibn YS, Tata F, Abdulganiyu G, Jamilu M, Tom MG. Evaluation of the relative incidence of adverse effects leading to treatment discontinuation of recommended antihypertensive drugs. Int Res J Pharm 2013;4(6):58-61.
76. Basak SC, Ravi K, Manavalan R, Sahoo K. A study of adverse drug reaction to antihypertensive drugs perceived by patients in a rural hospital. Indian J Pharm Sci 2004;66(6):814-7.
77. Dudala SR, Arlappa N. An updated Prasad's socio economic status classification for 2013. Int J Res Dev Health 2013;1(2):26-8.
78. Etuk E, Isezuo SA, Chika A, Akuche J, Ali M. Prescription pattern of antihypertensive drugs in a tertiary health institution in Nigeria. Ann Afr Med 2008;7(3):128-32.

79. Kousalya K, Chirumamilla S, Manjunath S, Ramalakshmi S, Saranya P, Chamundeeswari D. Prescribing trend of antihypertensive drugs in hypertensive and diabetic hypertensive patients. Asian J Pharm Clin Res 2012;5(4):22-3.
80. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL et al. The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. J Am Med Assoc 2003;289(19):2560-72.
81. Hypertension: Clinical management of primary hypertension in adults- NICE guideline: Aug 2011. [Internet]. 2012 [cited 2012 Sep 20]. Available from: http://www.nice.org.uk/nicemedia/live/13561/56008/56008.pdf.
82. Quick JD, Hogerzeil HV, Velasquez G, Rago L. Twenty-five years of essential medicines. Bull World Health Organ 2002;80(11):913-4.
83. Haile DB, Ayen WY, Tiwari P. Prevalence and assessment of factors contributing to adverse drug reactions in wards of a tertiary care hospital, India. Ethiop J Health Sci 2013;23(1):39-48.

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Phone No: 04651-280866. Fax No. 04651-280740

Institutional Human Ethics Committee

Ref. No. SMIMS/IHEC/2013/A/22 **Date: 1st July 2013**

Certificate

This is to certify that the Research Protocol Ref. No. **SMIMS/IHEC/2013/A/22,** entitled "A Study of Drug Utilization Pattern and Adverse Drug Reaction Profile of Antihypertensive Drugs Prescribed in SMIMS" submitted by Dr. A. Navaneeth, Postgraduate of Department of Pharmacology, SMIMS has been approved by the Institutional Human Ethics Committee at its meeting held on 30th of May 2013.

[This Institutional Human Ethics Committee is organized and operates according to the requirements of ICH-GCP/GLP guidelines and requirements of the Amended Schedule-Y of Drugs and Cosmetics Act, 1940 and Rules 1945 of Government of India.]

SRI MOOKAMBIKA INSTITUTE OF MEDICAL SCIENCES IHEC Date. 03/07/2013 KULASEKHARAM

Dr. Rema Menon. N
Member Secretary
Institutional Human Ethics Committee
Professor of Pharmacology and HOD
SMIMS, Kulasekharam (K.K District)
Tamil Nadu -629161

SREE MOOKAMBIKA INSTITUTE OF MEDICAL SCIENCES

KULASEKHARAM, Kanyakumari District Tamilnadu-629161

Institutional Human Ethics Committee [IHEC]

Date: 12th May 2014

Dr. Navaneeth A, Postgraduate student, Department of Pharmacology of this Institution had applied for change in title (Letter dated 10/05/2014) for the study entitled "A Study of Drug Utilization Pattern and Adverse Drug Reaction Profile of Antihypertensive Drugs Prescribed in SMIMS." This is required as per the regulations of the Tamil Nadu Dr. M.G.R Medical University where the name of the institute should not be used in the title of the study. Hence the candidate is permitted to change the title as **"A Study of Drug Utilization Pattern and Adverse Drug Reaction Profile of Antihypertensive Drugs Prescribed in A Tertiary Care Hospital."** This is to carry out the study in the approved period given by the IHEC.

SREE MOOKAMBIKA INSTITUTE OF MEDICAL SCIENCES ★ KULASEKHARAM ★
IHEC Date. 12/05/2014

Dr. Rema Menon. N
Member Secretary
Institutional Human Ethics Committee
SMIMS, Kulasekharam [K. K District]
Tamilnadu -629161

CONSENT FORM

PART 1 OF 2

INFORMATION FOR PARTICIPANTS OF THE STUDY

DEAR VOLUNTEERS,

We welcome you and thank you for your keen interest in participation in this research project. Before you participate in this study, it is important for you to understand why this research is being carried out. This form will provide you all the relevant details of this research. It will explain the nature, the purpose, the benefits, the risks, the discomforts, the precautions and the information about how this project will be carried out. It is important that you read and understand the contents of the form carefully. This form may contain certain scientific terms and hence, if you have any doubts or if you want more information, you are free to ask the study personnel or the contact person mentioned below before you give your consent and also at any time during the entire course of the project.

1. **Name of the Principal Investigator:** **Dr. A. Navaneeth**
Postgraduate
Department of Pharmacology
SMIMS, Kulasekharam

2. Name of the Guide: **Dr. Rema Menon. N (MD)**
Professor and Head
Department of Pharmacology
SMIMS, Kulasekharam

3. Name of the Co-Guides: **Dr. Kaniraj Peter (MD)**
Professor and Head
Department of Medicine
SMIMS, Kulasekharam

Dr. Madhavrao (MD)
Assistant Professor
Department of Pharmacology
SMIMS, Kulasekharam

4. Institute:

Sree Mookambika Institute of Medical Sciences, Kulasekharam 629161, Kanyakumari district, Tamilnadu.

5. Title of the study:

A Study of Drug Utilization Pattern and Adverse Drug Reaction Profile of Antihypertensive Drugs Prescribed in A Tertiary Care Hospital.

6. Background information:

Prevalence of hypertension is progressing rapidly worldwide. Response to antihypertensive drugs varies in different population. Drug utilization research establishes the current trend in the use of antihypertensive drugs and adverse drug reaction including the new drug and to identify irrational prescription. Irrational prescription can affect the adherence to drugs thereby not reaching therapeutic goal ultimately rising the economic burden. Since you are diagnosed to be hypertensive and on treatment with antihypertensive drugs it is proposed to do the study to evaluate the drug utilization pattern and adverse drug reactions of antihypertensive drugs in the Medicine department of this institution.

7. Aims and objectives:

To assess the following in the Department of Medicine, Sree Mookambika Institute of Medical Sciences, Kulasekharam, Tamilnadu during the period from October 2013 to March 2014:

i. The pattern of prescription of antihypertensive drugs as monotherapy and combination therapy

ii. The pattern by brand name and generic names

iii. The pharmacoeconomics of antihypertensive drugs prescribed

iv. Rationality of antihypertensive drugs prescribed

v. The adverse drug reaction profile of antihypertensive drugs

8. Scientific justification of the study:

Drug utilization research establish current trend in the use of antihypertensive drugs and adverse drug reactions including the new drug and to identify irrational prescription. Irrational prescription can affect the adherence to drugs thereby not reaching therapeutic goal ultimately rising the economic burden. Till date no study on drug utilization pattern and adverse drug reaction profile of antihypertensive drugs is conducted in this institution. Hence it has been proposed to conduct the study to evaluate the drug utilization pattern and adverse drug reaction profile of antihypertensive drugs in the Medicine department of this institution.

9. Procedure for the study:

The study will be carried out after getting informed written consent from each participant. The study will not have any impact on the treatment given by physician. Study will be carried out in collaboration with the Medicine department. Enrolled subject name, age, sex, co-morbid condition and treatment if any will be recorded in a predesigned case record form. Details of the prescribed antihypertensive drug(s) will be recorded. Conclusion of the study will be made from the details in the case record form.

10. Expected risks for the participants:

This study does not involve any risk to the participant**.**

11. Expected benefits of research for the participants:

This study does not provide any direct benefit to the participant, however the data obtained from the study will be useful for better medical health care in the future.

12. Maintenance of confidentiality:

Will be maintained.

13. Why have I been chosen to be in this study?

You are diagnosed as hypertensive and prescribed with antihypertensive drugs, hence according to the inclusion and exclusion criteria you are recruited into this study.

14. Agreement of Compensation to the participants (In case of a study related injury):

Not applicable

16. Anticipated prorated payment, if any, to the participant(s) of the study:

No

17. Can I withdraw from the study at any time during the study period?

The study participant can withdraw from the study at any time and will not involve any penalty or loss of benefits to which the participant is otherwise entitled.

18. If there is any new findings / information, would I be informed?

Yes

19. Expected duration of the Participant's participation in the study:

1 day

20. Any other pertinent information:

No

21. Whom do I contact for further information?

For any study related queries, you are free to contact

Dr. A. Navaneeth

Post Graduate

Department of Pharmacology

SMIMS

Mobile number: 9626421444

Email:navneetpraveen@gmail.com

Place: Kulasekharam **Signature of the Principal Investigator**

Date :

Signature of the Participant

CONSENT FORM

PART 2 OF 2

PARTICIPANTS CONSENT FORM

The details of the study have been explained to me in writing and the details have been fully explained to me. I am aware that the results of the study may not be directly beneficial to me but will help in the advancement of medical sciences. I confirm that I have understood the study and had the opportunity to ask questions. I understood that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without the medical care that will normally be provided by the hospital being affected. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). I have been given an information sheet giving details of the study. I fully consent to participate in the study titled **'A study of drug utilization pattern and adverse drug reaction profile of antihypertensive drugs prescribed in SMIMS'.**

Serial no/Reference no:

Name of the Participant: **Address of the Participant:**

Signature of the participant

Witnesses:

1.

2.

Date:

Place: Kulasekharam

Sree Mookambika Institute of Medical Sciences

Department of Pharmacology

Case Record Form

Serial number:

Name: Date:

Age: Sex: M / F OPD No. :

Occupation: Socioeconomic status:

Address with contact number:

Diagnosis:

Duration: BP: BP (Previous visit):

Any co-existing disease? Yes / No. (If yes then details)

Any other concurrent medication used? Yes / No. (If yes then details)

Prescription details:

S.No	Name of the drug prescribed	Formulation	Dose	Route	Frequency	Duration	Before/After Food	Cost in INR

Adverse drug reactions reported by patients:
(If adverse reaction experienced details will be filled up in CDSCO ADR form)

Adverse drug reaction	Experienced/Not experienced
Nausea, Vomiting	
Dizziness, Headache	
Cough	
Oedema	
Erectile dysfunction	
Diarrhoea	
Dyspnoea	
Fatigue	
Hallucinations	
Any other ADRs	

Place: Kulasekharam

Date: **Signature of the Principal Investigator**

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

For VOLUNTARY reporting of Adverse Drug Reactions by healthcare professionals

INDIAN PHARMACOPOEIA COMMISSION
(National Coordination Centre-Pharmacovigilance Programme of India)
Ministry of Health & Family Welfare
Government of India
Sector-23, Raj Nagar, Ghaziabad-201002
www.ipc.nic.in

(AMC/ NCC Use only)
AMC Report No.
Worldwide Unique

A. PATIENT INFORMATION

1. Patient Initials _____

2. Age at time of Event or date of birth _____

3. Sex ☐ M ☐ F

4. Weight ___Kgs

12. Relevant tests / laboratory data with dates

B. SUSPECTED ADVERSE REACTION

5. Date of reaction started (dd/mm/yyyy)

6. Date of recovery (dd/mm/yyyy)

7. Describe reaction or problem

13. Other relevant history including pre-existing medical conditions (e.g. allergies, race, pregnancy, smoking, alcohol use, hepatic/ renal dysfunction etc)

14. Seriousness of the reaction

- ☐ Death (dd/mm/yyyy)
- ☐ Life threatening
- ☐ Hospitalization/prolonged
- ☐ Disability
- ☐ Congenital-anomaly
- ☐ Required intervention to prevent permanent impairment / damage
- ☐ Other (specify)

15. Outcomes

- ☐ Fatal
- ☐ Continuing
- ☐ Recovering
- ☐ Recovered
- ☐ Unknown
- ☐ Other (specify)

C. SUSPECTED MEDICATION(S)

S.No	**8.** Name (brand and /or generic name)	Manufacturer (if known)	Batch No./ Lot No. (if known)	Exp. Date (if known))	Dose used	Route used	Frequency	Therapy dates (if known, give duration)		Reason for use of prescribed for
								Date started	Date stopped	
i.										
ii.										
iii.										
iv.										

S.No As per C	**9.** Reaction abated after drug stopped or dose reduced					**10.** Reaction reappeared after reintroduction				
	Yes	No	Unknown	NA	Reduced dose	Yes	No	Unknown	NA	If reintroduced dose
i.										
ii.										
iii.										
iv.										

11. Concomitant medical product including self medication and herbal remedies with therapy dates (exclude those used to treat reaction)

D. REPORTER (see confidentiality section on first page)

16. Name and Professional Address :_____

Pin code: _____E-mail _____

Tel. No. (with STD code): _____

Occupation _____Signature _____

17. Causality Assessment

18. Date of this report (dd/mm/yyyy)

Abbreviations	
ACE	:Angiotensin converting enzyme
ADCR	:Adverse cutaneous drug reactions
ADR	:Adverse drug reaction
AIPs	:Aldosterone-induced proteins
Ang I	:Angiotensin I
Ang II	:Angiotensin II
ANS	:Autonomic nervous system
AP	:Action potential
ARB	:Angiotensin receptor blocker
AT1	:Angiotensin II receptor, type 1
AT2	:Angiotensin II receptor, type 2
BMI	:Body mass index
BP	:Blood pressure
BPH	:Benign prostatic hyperplasia
CAD	:Coronary artery disease
cAMP	:Cyclic adenosine monophosphate
CBA	:Cost benefit analysis
CCB	:Calcium channel blocker
CDSCO	:Central Drugs Standard Control Organization
CEA	:Cost effectiveness analysis
CHF	:Chronic heart failure
CMA	:Cost minimization analysis
COPD	:Chronic obstructive pulmonary disease
COX-2	:Cyclooxygenase-2
CUA	:Cost utility analysis
CVA	:Cerebrovascular accident
DA	:Dopamine
DASH	:Dietary Approaches to Stop Hypertension
DCT	:Distal convoluted tubule

DHPs	:Dihydropyridines
DM	:Diabetes mellitus
DUS	:Drug utilization studies
ECF	:Extracellular fluid
EDL	:Essential drug list
FDC	:Fixed dose combination
G proteins	:Guanosine nucleotide binding regulatory proteins
GFR	:Glomerular filtration rate
HDL	:High density lipoprotein
ISH	:International Society of Hypertension
JNC 7	:Joint National Committee-7
LDL	:Low density lipoprotein
LVH	:Left ventricular hypertrophy
MAO	:Monoamine oxidase
MI	:Myocardial infarction
NICE	:National Institute for Health and Clinical Excellence
NSAIDS	:Nonsteroidal Antiinflammatory Drugs
PVR	:Peripheral vascular resistance
RAAS	:Renin angiotensin aldosterone system
TPR	:Total peripheral resistance
UMC	:Uppsala Monitoring Centre
VMAT	:Vesicular monoamine transporter
WHO	:World health organisation